Associazione Coagulopatici Emofilici Piemontesi "Massimo Chesta"
PROMUOVE IL CONGRESSO

COAGULOPATIE CONGENITE:
bisogni espressi, organizzazione
del Centro Multidisciplinare di Città della Salute

Torino, 25 novembre 2017
Starhotels Majestic

NUOVI FARMACI A LUNGA EMIVITA

Dott.ssa Irene Ricca

Centro di Riferimento Regionale per le Malattie Emorragiche e Trombotiche Ereditarie In Età Pediatrica

Ospedale Infantile Regina Margherita - Torino

LA PROFILASSI OGGI

- Obiettivo comune: trough level > 1% ***PER TUTTI?***
  - Alcuni pazienti comunque sintomatici
  - Pazienti che necessitano di livelli più elevati (sport…)
  - Malattie eterogenea: ➔ *individualizzazione della profilassi*
- Ampia variabilità nella PK dei fattori
- Emivita dei fattori convenzionali relativamente breve (18-24h):
  ➔ *frequenti infusioni di fattore*

  - Personalizzazione delle dosi
  - Personalizzazione del numero di infusioni settimanali

NUOVI FARMACI A LUNGA EMIVITA

Sviluppo di nuove molecole di FVIII e FIX a emivita prolungata: Partners

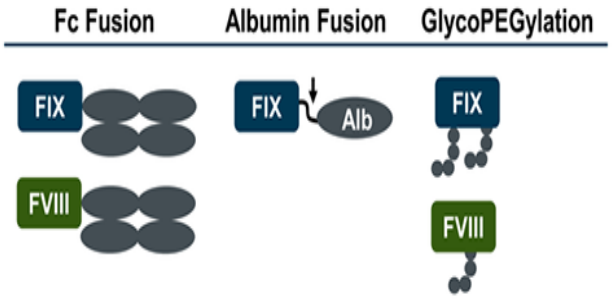
MOLECOLE DI FUSIONE

Fusione con frammento Fc delle IgG:
rFVIII-Fc (Elocta®)
rFIX-Fc (Alprolix®)

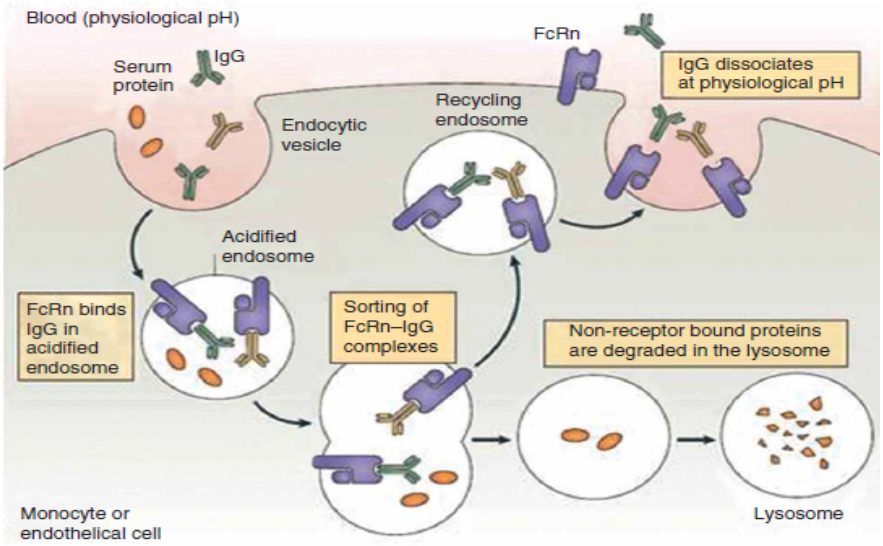
Fusione con albumina umana ricombinante.
Solo FIX
rFIX-FP (Idelvion®)

PEGHILAZIONE

Aggiunta di polietilen glicol (PEG) catene di 5-60 kDa:
BAX 855 (Adynovi®),
Bay 94-9027, N8-GP



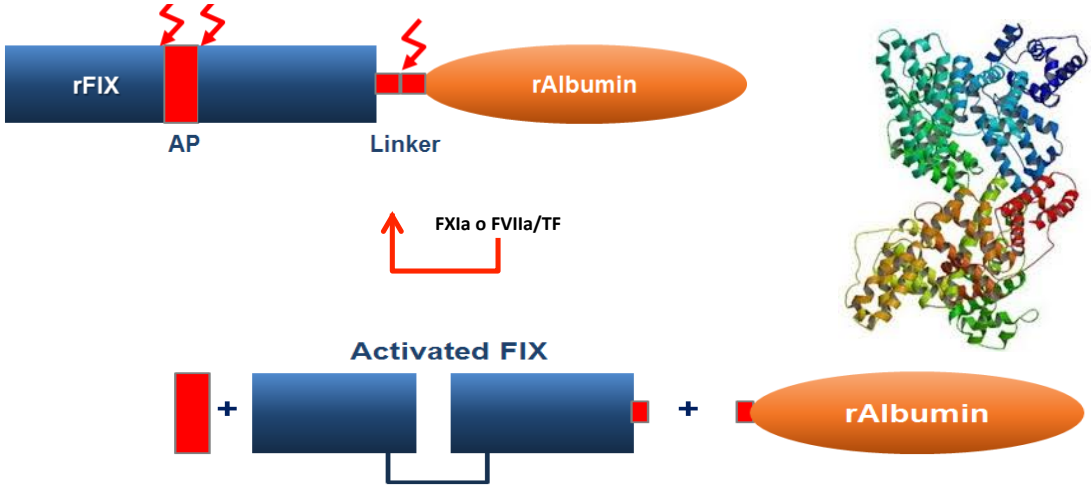
FcRn recycling pathway



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.

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.

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

Haemophilia 2016; 22:487-98

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

Table 1. Enhanced half-life factor VIII products: manufacturing characteristics and pharmacokinetics.

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®

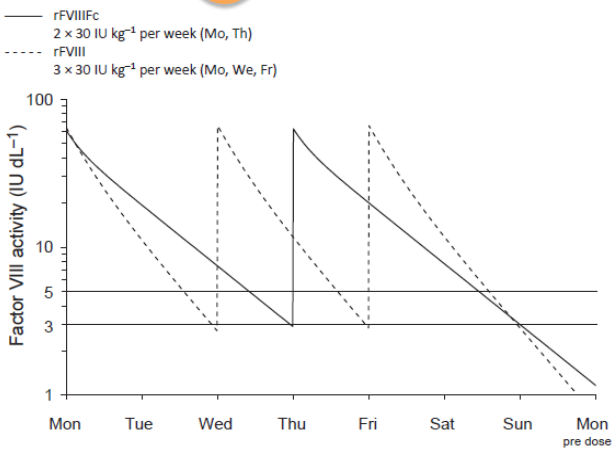
Incremento dell'emivita: 1.5-1.7

Haemophilia, 2016

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



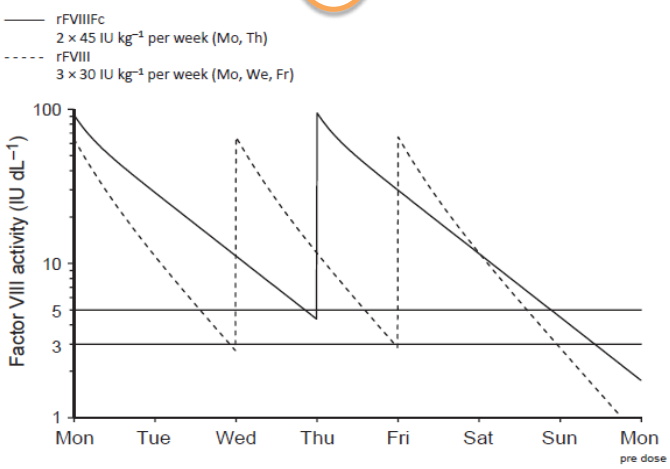
Livelli di FVIII simili utilizzando la stessa dose e una iniezione in meno alla settimana.

Haemophilia, 2016

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‡§

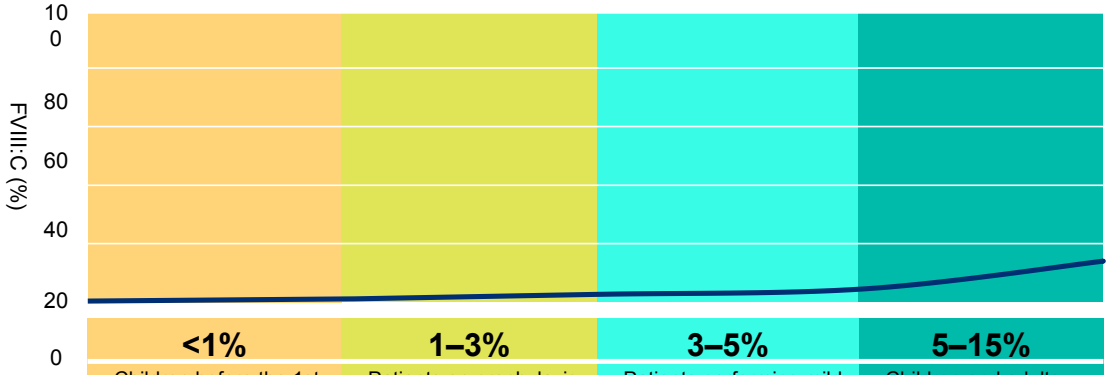
Factor	Injections/ week	Dose (IU/kg/ week)	Peak (IU/dL)	Troughs (IU/dL)	Time below 5 IU/dL/week (days)	Time below 3 IU/dL/week (days)	Time below 1 IU/dL/week (days)
rFVIIIFc	2	90	93	4.4/1.7	1.3	0.6	0
rFVIII	3	90	65	2.7/2.8/0.7	2.3	1.2	0.2



Livelli di FVIII più elevati utilizzando una dose maggiore ma con un uguale consumo settimanale di FVIII e una infusione in meno alla settimana

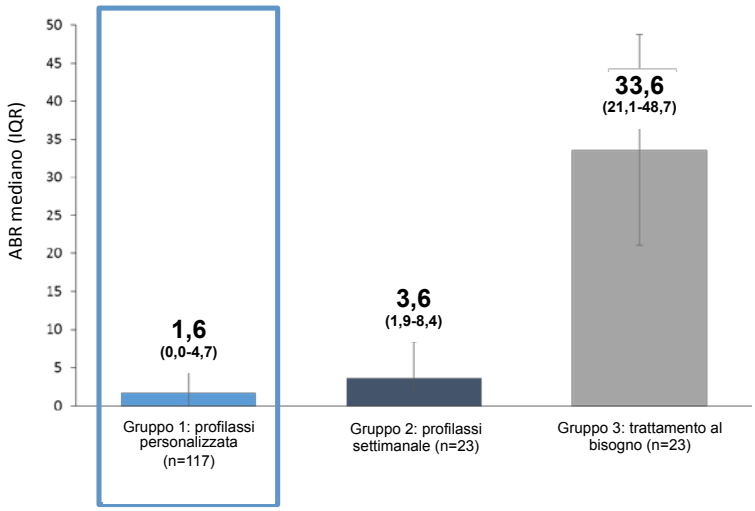
Target trough FVIII levels for personalised treatment

A Delphi consensus statement – Personalised prophylaxis



<1%	1–3%	3–5%	5–15%
1. Children before the 1st bleed 2. Patients treated on-demand 3. Patients on prophylaxis with sedentary lifestyles not bleeding	1. Patients on prophylaxis not bleeding 2. Patients with mild bleeding 3. Adult and paediatric patients with sedentary lifestyles 4. Children <2 years or until the 1st bleed 5. Patients with moderate haemophilia	1. Patients performing mild physical activities 2. Patients with target joints or severe progressive haemophilic arthropathy 3. Patients presenting bleeding despite prophylaxis at a lower target threshold 4. Children on primary prophylaxis 5. Patients with previous life- threatening bleeding events	1. Children and adults performing high-risk activities 2. Patients presenting bleeding despite prophylaxis at a lower target threshold 3. Patients with target joints or severe arthropathy presenting bleeding despite prophylaxis at a lower target threshold 4. Patients with severe comorbidities

Basso ABR con Elocta in profilassi personalizzata



Regime posologico: **50 UI/KG**;
25-65 UI/kg, ogni 3-5 giorni
Durata mediana (min, max): **32,1 (9 - 54) settimane**

30% dei pazienti ogni 5 giorni

Mahlangu et al. Blood 2014

FIX – prodotti ad Enhanced half-life (EHL)

Table 2. Enhanced half-life factor IX products: manufacturing char

Incremento dell'emivita a 60-90 ore

Product	Company	Cell line	Biochemical strategy	Age	Subjects	(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 Median (range) 8 (6–11)	13	Mean (95% CI) 0.72 (0.61–0.84)	Mean (95% CI) 70.3 (61.0–81.2)
				<6 Median (range) 2 (1–4)	11	Mean (95% CI) 0.59 (0.52–0.68)	Mean (95% CI) 66.5 (55.9–79.1)
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)

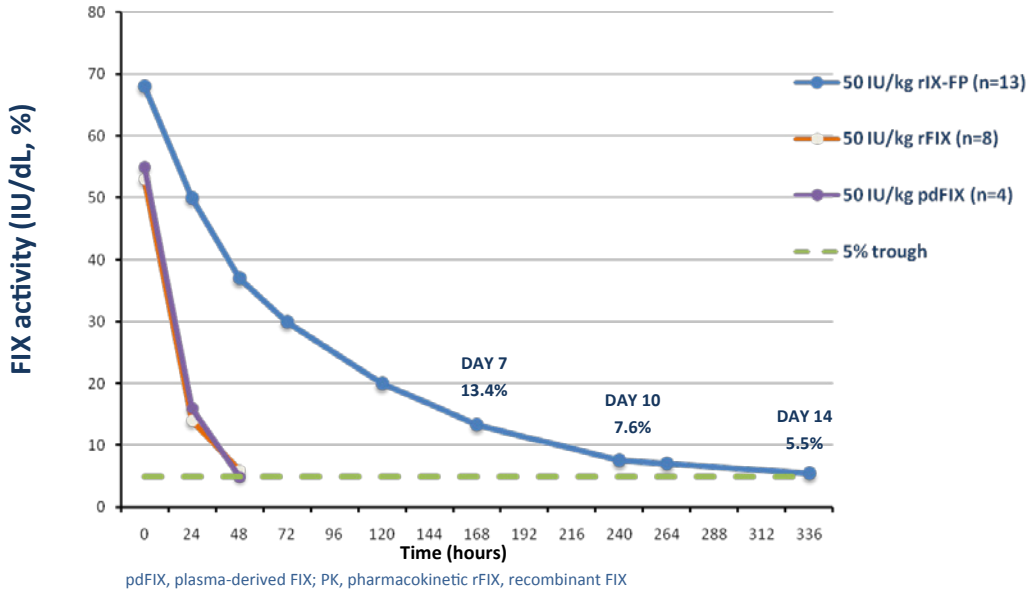
ALPROLIX®

IDELVION®

Haemophilia 2016; 22:487-98

EHL-rFIX vs FIX convenzionali: rFIX-FP 50UI/kg

Baseline-corrected FIX activity levels after administration of 50 IU/kg rFIX-FP, rFIX or pdFIX (PK population)



pdFIX, plasma-derived FIX; PK, pharmacokinetic rFIX, recombinant FIX

Santagostino *et al. Blood* 2012;120:2405–11.

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

Emofilia B la profilassi oggi...

EHL-rFVIII/IX : quale scelta terapeutica?
↓ infusioni vs. ↑ livello minimo vs. entrambi

Basso numero di infusioni mantenendo concentrazione minima > 1%	Infusioni più frequenti con livelli minimi più alti
Pazienti meno attivi Bambini piccoli a inizio profilassi Scarso accesso venoso	Pazienti più attivi Soggetti con un buon accesso venoso Farmaci pro emorragici

Per ogni paziente si sceglierà uno o l'altro o un ibrido, a seconda di stile di vita e bisogni

↗ individualizzazione della profilassi

Semin Thromb Hemost 2016; 42:526-32

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

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

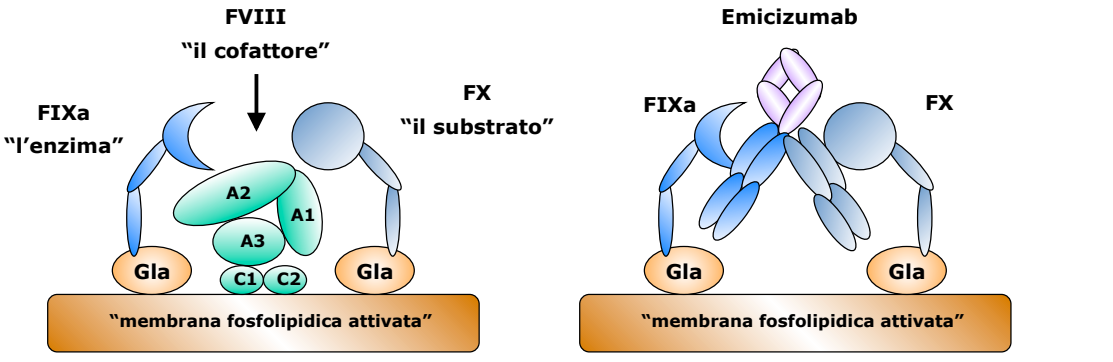
Stabillizzazione del coagulo: FXIII

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

Terapie non sostitutive: ACE910/Emicizumab

- ACE910/Emicizumab è un anticorpo ricombinante umano con doppia specificità per il FIXa ed il FX, che mima la funzione di cofattore del FVIII
- Emivita prolungata (4-5 settimane) ed un' alta biodisponibilità SOTTOCUTANEA
- Accorcia l'aPTT in modo dose-dipendente
- Studio in fase 3 in pazienti con emofilia e inibitori ad alto titolo

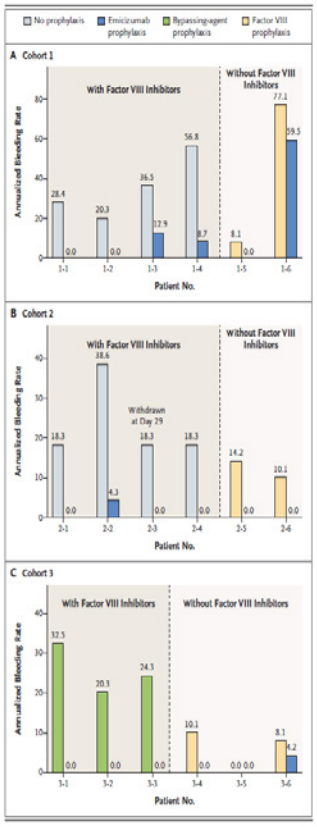


Muto A et al. *J Thromb Haemost* 2014;12:206–213
Uchida N et al. *Blood* 2016;127(13):1633–1641

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

FARMACI A LUNGA EMIVITA

- POTENZIALMENTE IN GRADO DI **SEMPLIFICARE LA GESTIONE DELLA MALATTIA** E CONSEGUENTEMENTE LA VITA DEI PAZIENTI

- **RIDUZIONE DELLA FREQUENZA DELLE INFUSIONI**
  - 30-35% PER I PAZIENTI CON EMOFILIA A
  - 50% PER I PAZIENTI CON EMOFILIA B
- AUMENTO DEI LIVELLI EMATICI DI FATTORE CARENTE CON **MINOR RISCHIO DI SANGUINAMENTO**
- MIGLIORE **RAZIONALIZZAZIONE DELLA TERAPIA** CON CONSEGUENTI RICADUTE POSITIVE ANCHE SULLA SPESA SANITARIA

Grazie!