Nuevas estrategias en el tratamiento de pacientes con inhibidor

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Conflict of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	Pfizer, Shire, NovoNordisk, Roche, Bayer, Sobi, Octapharma, Grifols.
Receipt of honoraria or consultation fees:	Pfizer, Shire, NovoNordisk, Roche, Bayer, CSL Behring, Sobi, Octapharma, Grifols
Participation in a company sponsored speaker's bureau:	No
Stock shareholder:	No
Spouse/partner:	No
Other support (please specify):	No


hemophilia
blood
disease
medical
anemia
research
laboratory
biomedical
prevention
professional
chemistry
formula
technology
experiment
awareness
illness
care
infection
thrombocytopenia
prothrombin
sample
pathologist
thrombocyte
healthcare
lab
hematocrit
hematology
patient
hemoglobin
plasma
chemicals
pharmacology
cells
clotting
physician
chemist
liquid
haematologists
test
treatment
diagnosis
analyzing
thrombin
health
structure
equipment
exam
leukemia
haemophilia
medicine
thalassemia
bleeding
transfusion
scientist
virus
genetic
medic
biologist
cell analysis
science
biomedicine
hematologist
disorder
pathology
scientific

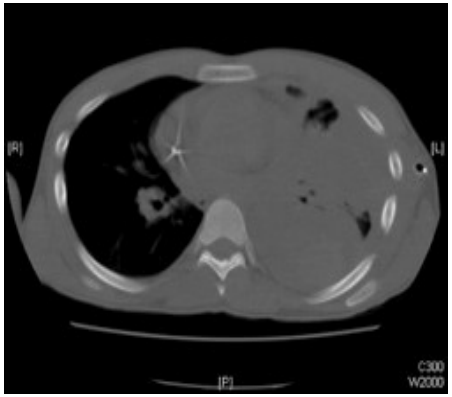
Introducción

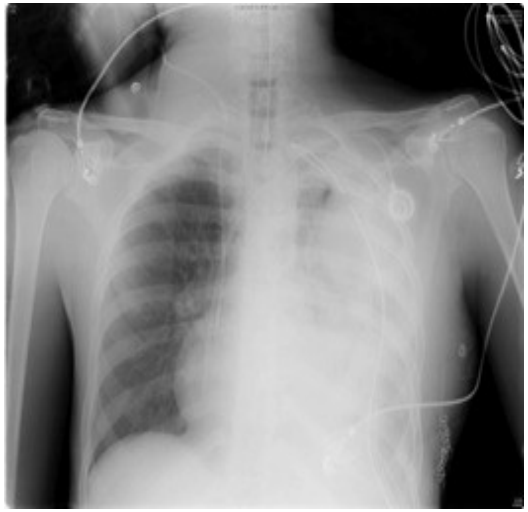
- El desarrollo de inhibidores es la complicación más importante del tratamiento de la hemofilia

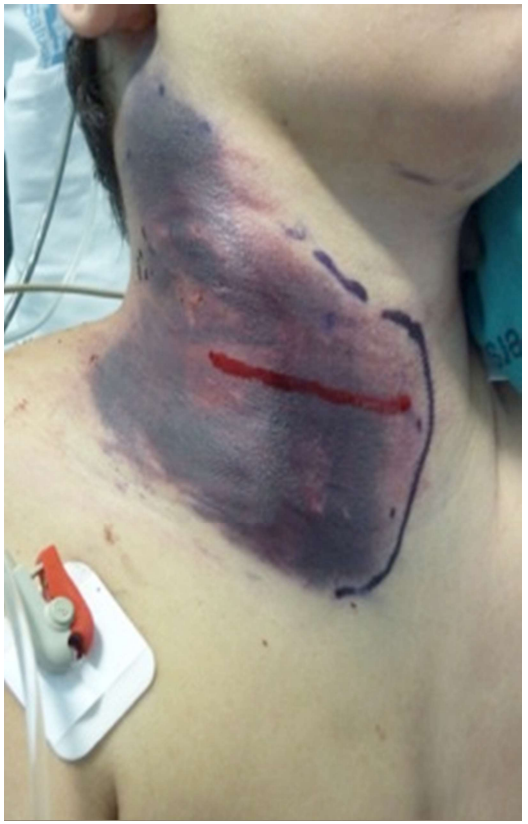
- Mejoras en el tratamiento ha supuesto una menor mortalidad…..

- Inhibidores están asociados a una alta morbilidad
  - Alta tasa de complicaciones hemorrágicas
  - Aumento de las discapacidades
  - Descenso de la calidad de vida
  - Alta mortalidad

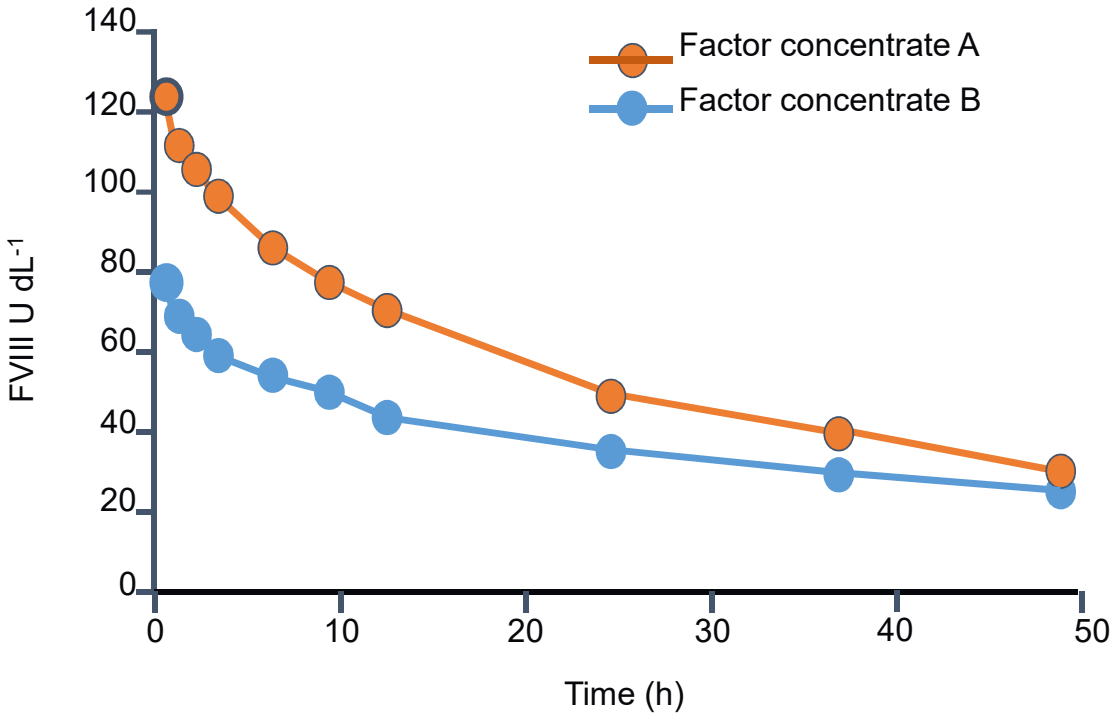
El problema





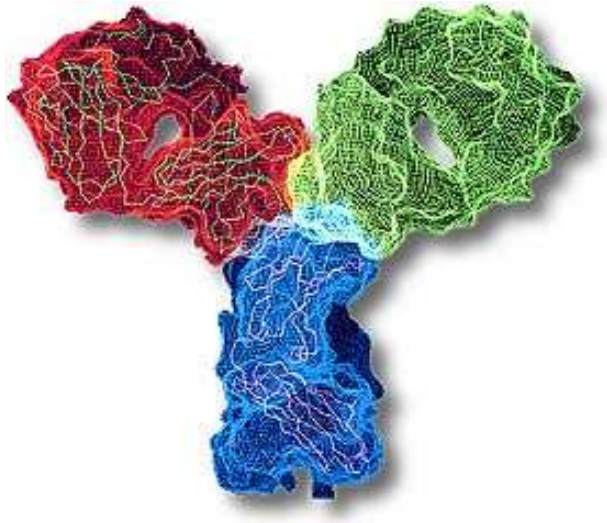


Terapia sustitutiva



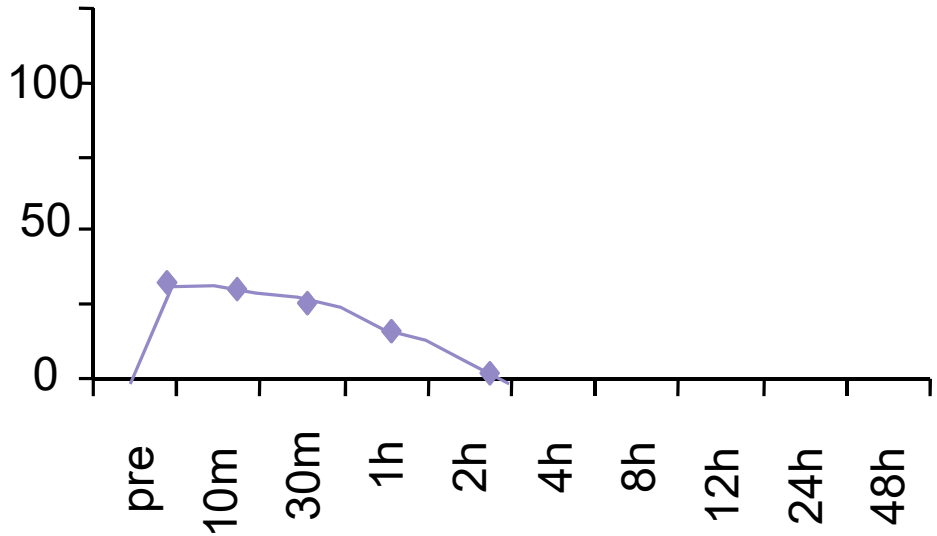
Complicación del tratamiento

- INHIBIDOR: Anticuerpo IgG de alta afinidad de naturaleza policlonal frente al FVIII o FIX de la coagulación



Desarrollo de inhibidores

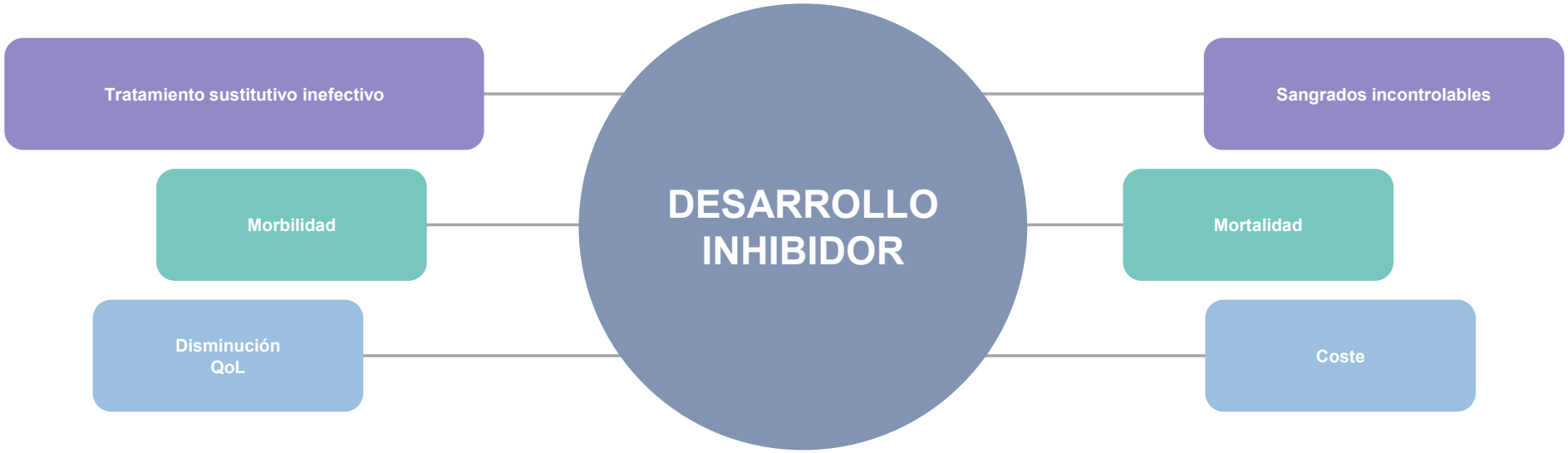
- Reduce vida media de los concentrados de factor
- Refractariedad a la terapia sustitutiva



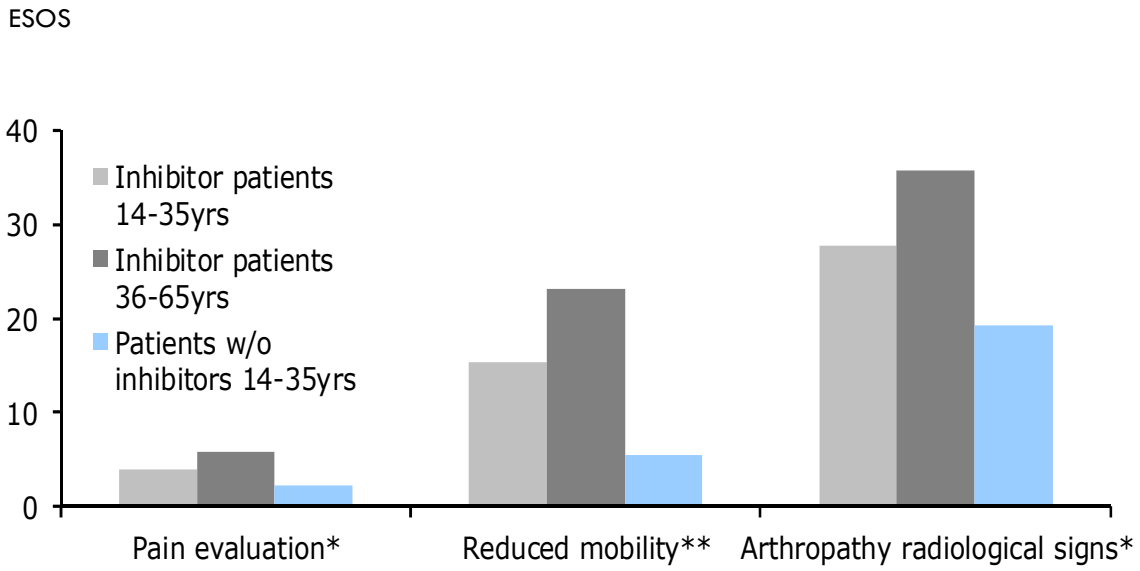
Incidencia

- Incidencia:
- Hemofilia A: 30 %
- Hemofilia B: 1-4 %
- Prevalencia:
- Hemofilia A: 10-12 %

Relevancia Inhibidor



Relevancia Inhibidor



*Pettersson classification, scores per joint ranging from 0 to 13
**Gilbert classification, scores per joint ranging from 0 for no pain to 3 for maximum pain and for clinical examination, scores per joint ranging from 0 to 12 for knees and ankles, 0 to 10 for hips and 0 to 8 for elbows and shoulders

Source: Morfini et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 2007;13:606–12

¿COMO TRATAR LOS PACIENTES CON HEMOFILIA E INHIBIDOR?

CON MUCHA DIFICULTAD

EXPERIENCIA

CONOCIMIENTO

Estrategias

EPISODIOS HEMORRÁGICOS

INMUNOTOLERANCIA

Episodios hemorrágicos

Tratamiento de los episodios hemorrágicos

Episodios hemorrágicos

- Bajo título de inhibidor o bajos respondedores (<5 U.B.)

  Concentrados factor VIII a altas dosis

- Alto título de inhibidor o altos respondedores (>5 U.B.)

  CCPA (Feiba®)

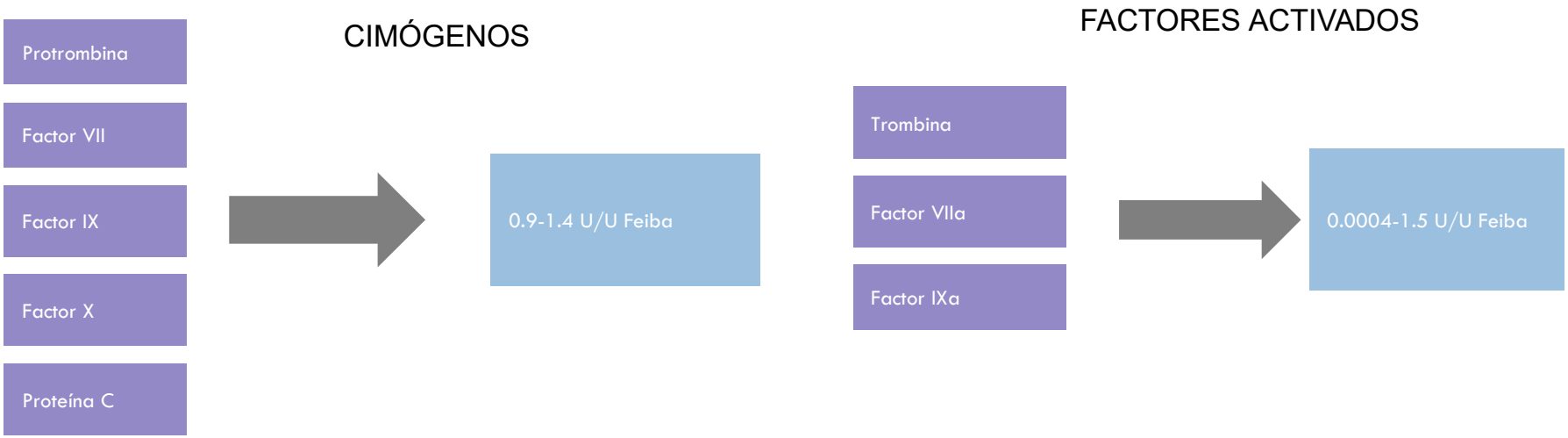
  rFVIIa (Novoseven®)

Episodios hemorrágicos

FEIBA

CCPa (FEIBA®)

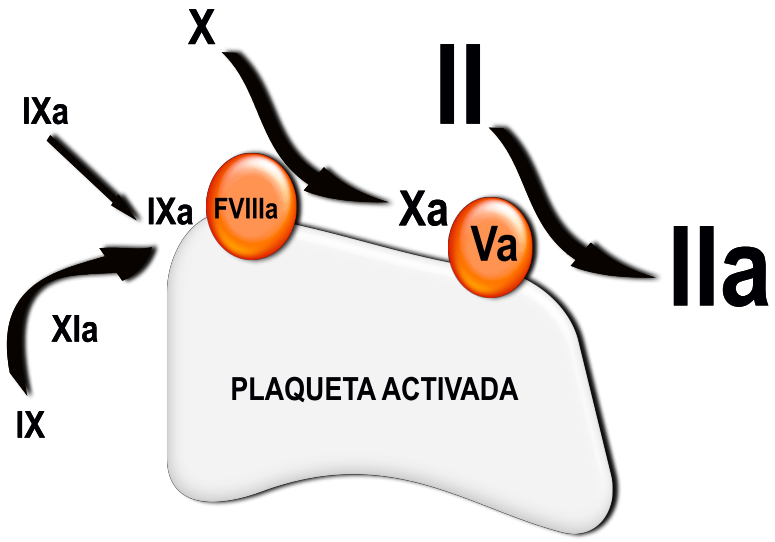
- CCPA (FEIBA®): Complejo protrombínico activado
  - FII, FVII, FIX, FX, pequeñas cantidades de FIXa, FXa y trombina y de FVIIa[1].

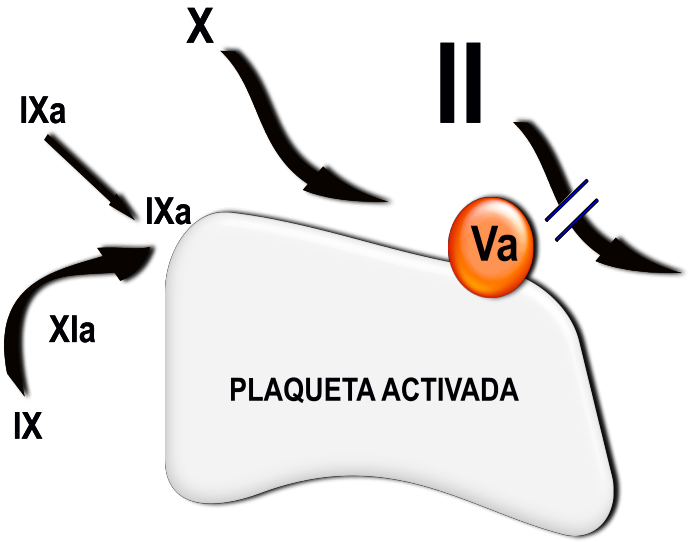


1. Gallistl S, et al. Blood Coagul Fibrinolysis. 2002;13(7):653-5.

CCPa (FEIBA®)

- CCPA (FEIBA®): Complejo protrombínico activado
  - Mecanismo de acción[1]:

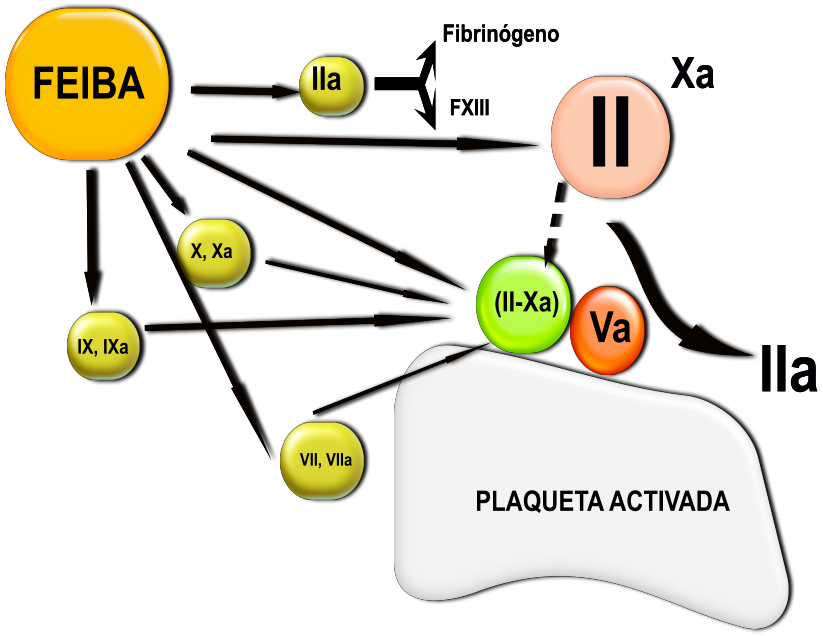




1. Hoffman M, Monroe DM. Thromb Res. 2010;125(Suppl 1):S6-18

CCPa (FEIBA®)

- CCPA (FEIBA®): Complejo protrombínico activado
  - Mecanismo de acción[1]:



1.Turecek PL, et al.Haemophilia. 2004 Sep;10 Suppl 2:3-9.
2. Gallisti S, et al. Blood Coagul Fibrinolysis. 2002;13(7):653-5.

CCPa (FEIBA®)

- CCPA (FEIBA®): Complejo protrombínico activado
  - Dosis:
    - 50-100 UI/Kg cada 8-12h
    - Se recomienda no sobrepasar 200-220 UI/kg día
    - La utilización de dosis altas en corto periodo tiempo

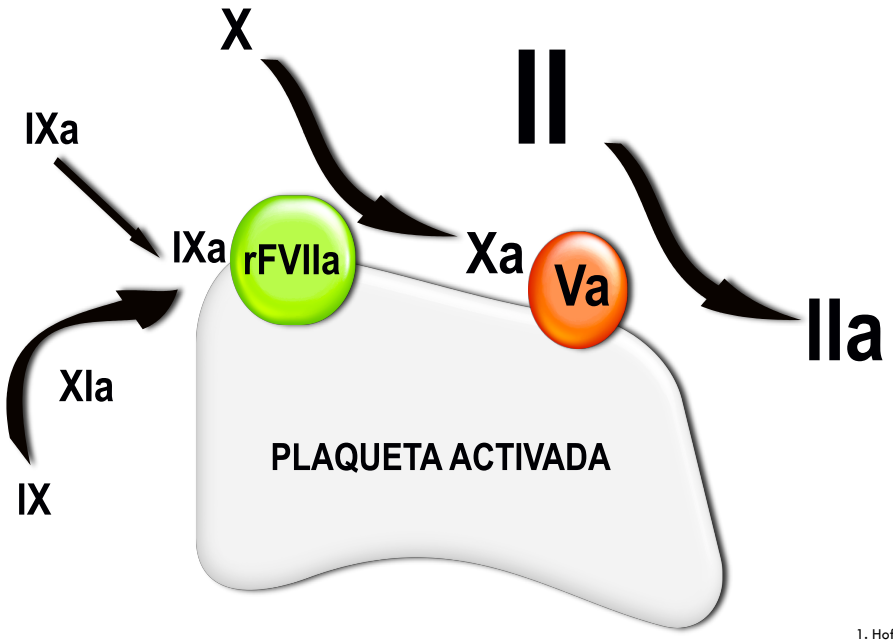
    - PAUTA INICIAL: 70-80 UI/Kg cada 8-12h

Episodios hemorrágicos

NovoSeven

rFVIIa (NovoSeven®)

- rFVIIa (NovoSeven®): Factor VII activado recombinante
  - Mecanismo de Acción:



1. Hoffman M, Monroe DM. Thromb Res. 2010;125(Suppl 1):S6-18

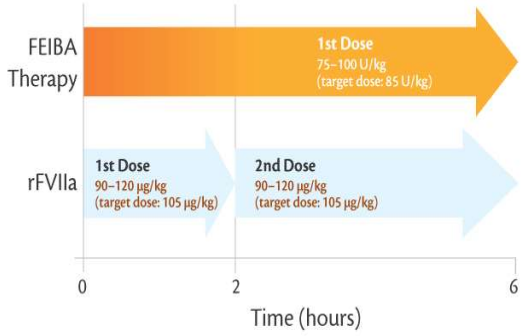
rFVIIa (NovoSeven®)

- rFVIIa (NovoSeven®): Factor VII activado recombinante
  - Dosis:
    - 90-120 µgr/kg cada 2 h
    - Utilización de dosis únicas de 270 µgr/Kg
    - La utilización de dosis altas en corto periodo tiempo

    - PAUTA INICIAL: 90-120 µgr/kg cada 2 h

CCPa vs rFVIIa

- Eficacia global comparable 80-90% [1-4].
- Estudio FENOC:
  - Astermark J, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood. 2007 Jan 15;109(2):546-51.

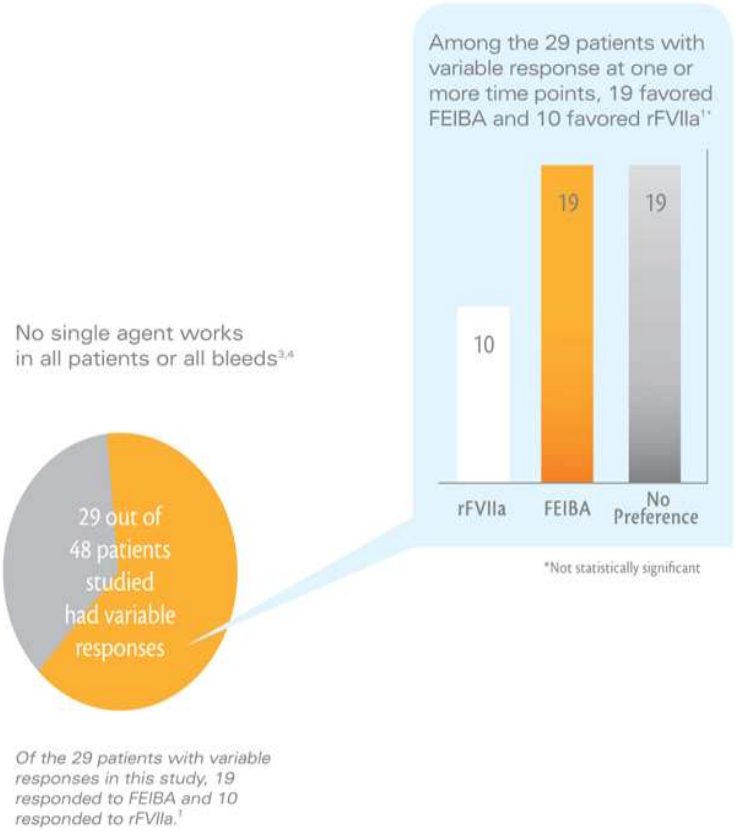


- A las 6 horas: FEIBA 80.9% vs rFVIIa 78.7%.
- No enmascaramiento
- Primeras horas evaluación más fiable

1.Berntorp E. Haemophilia. 2009;15(1):3-10.
2. Negrier C et al. Thromb Haemost. 1997;77(6):1113-9.
3. Tjonnfjord GE, Holme PA.. Vasc Health Risk Manag. 2007;3(4):527-31.
4. Iorio A et al. Cochrane Database of Systematic Review 2010, Issue 8. CD:004449

CCPa vs rFVIIa

- Estudio FENOC[1] :
  - 29 pacientes eficacia discordante
  - 19 respondían mejor CCPA y 10 rFVIIa
  - Este grupo había tenido mayor número de sangrados en el año previo: articulación diana
  - Diferentes mecanismos explican la variabilidad
  - VARIABILIDAD INTER E INTRAPACIENTE



1. Astermark J, et al. Blood. 2007 Jan 15;109(2):546-51.

Elección agente

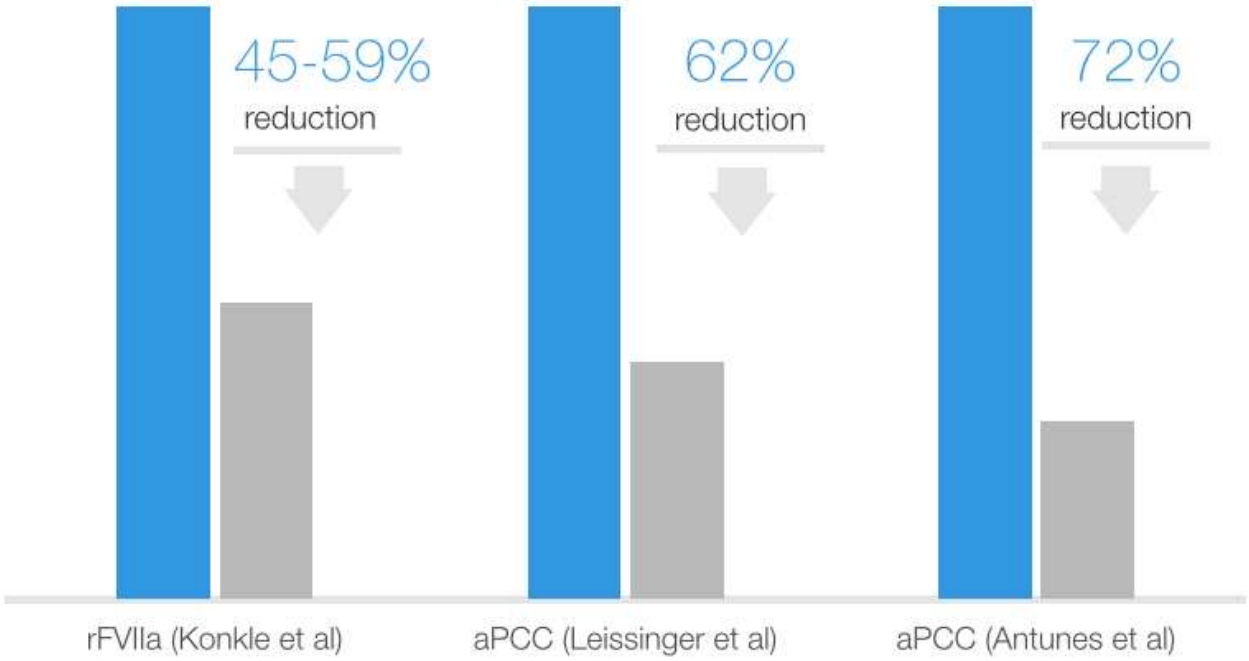
Tratamiento de primera línea
CCPA: 70-80 UI/Kg
rFVIIa: 90-120 µg/Kg

- Disponibilidad
- Experiencia
- Éxito previo
- Edad
- ITI

Profilaxis

Profilaxis en pacientes con inhibidor

Profilaxis


45-59%
reduction
62%
reduction
72%
reduction
rFVIIa (Konkle et al)
aPCC (Leissinger et al)
aPCC (Antunes et al)

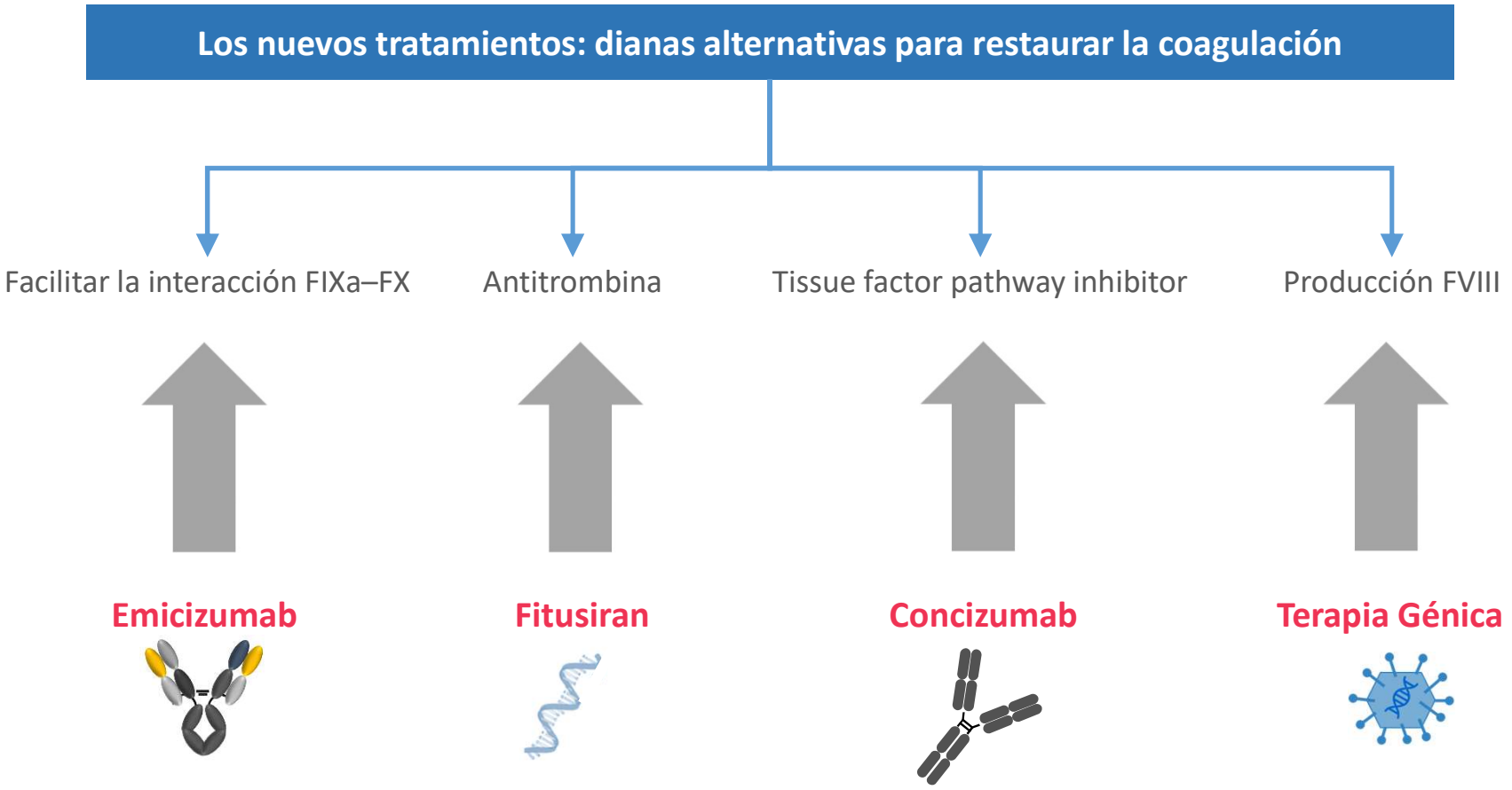
Profilaxis

- Targeted inhibitor patients populations[1]:

Target join	Life-threatening bleed	Major orthopaedic surgical procedure	Multiple bleeds affecting school/work performance

1.Young G et al. When should prophylaxis therapy in inhibitor patients be considered?. Haemophilia 2011;17:e849–e857.

Los nuevos tratamientos actúan en diferentes partes de la cascada de la coagulación con el fin de restaurar una hemostasia eficiente



Ac biespecífico: Emicizumab

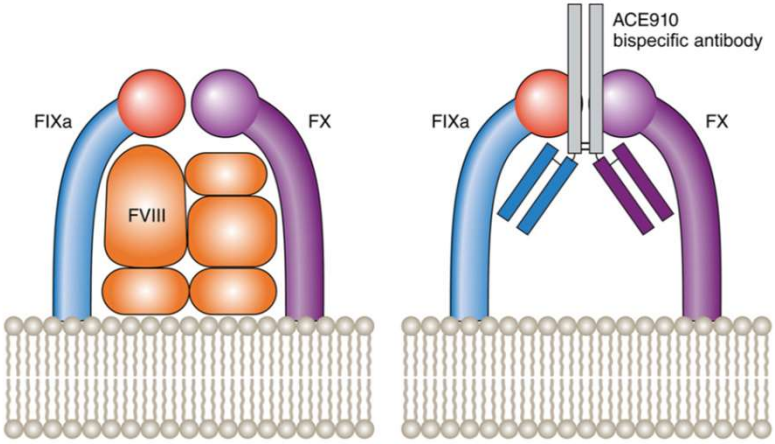
● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Uchida et al, page 1633

Hemophilia A treatment: disruptive technology ahead

Michael Makris UNIVERSITY OF SHEFFIELD

In this issue of *Blood*, Uchida et al report the first-in-human use of a new nonsubstitutive therapy for hemophilia A that can potentially be disruptive to the way hemophilia is treated.[1]



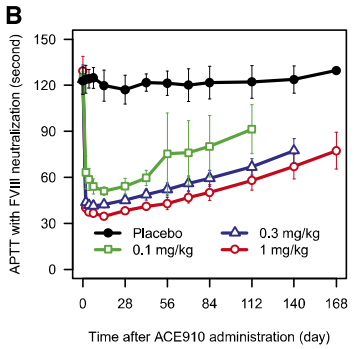
Plenary Paper

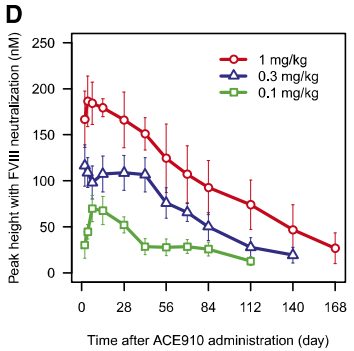
CLINICAL TRIALS AND OBSERVATIONS

A first-in-human phase 1 study of ACE910, a novel factor VIII–mimetic bispecific antibody, in healthy subjects

Naoki Uchida,[1,2] Takehiko Sambe,[1,2] Koichiro Yoneyama,[3] Naoki Fukazawa,[3] Takehiko Kawanishi,[3] Shinichi Kobayashi,[1] and Midori Shima[4]

[1]Showa University Clinical Research Institute for Clinical Pharmacology and Therapeutics, Tokyo, Japan; [2]Department of Pharmacology, School of Medicine, Showa University, Tokyo, Japan; [3]Translational Clinical Research Division, Chugai Pharmaceutical Co, Ltd., Tokyo, Japan; and [4]Department of Pediatrics, Nara Medical University, Nara, Japan





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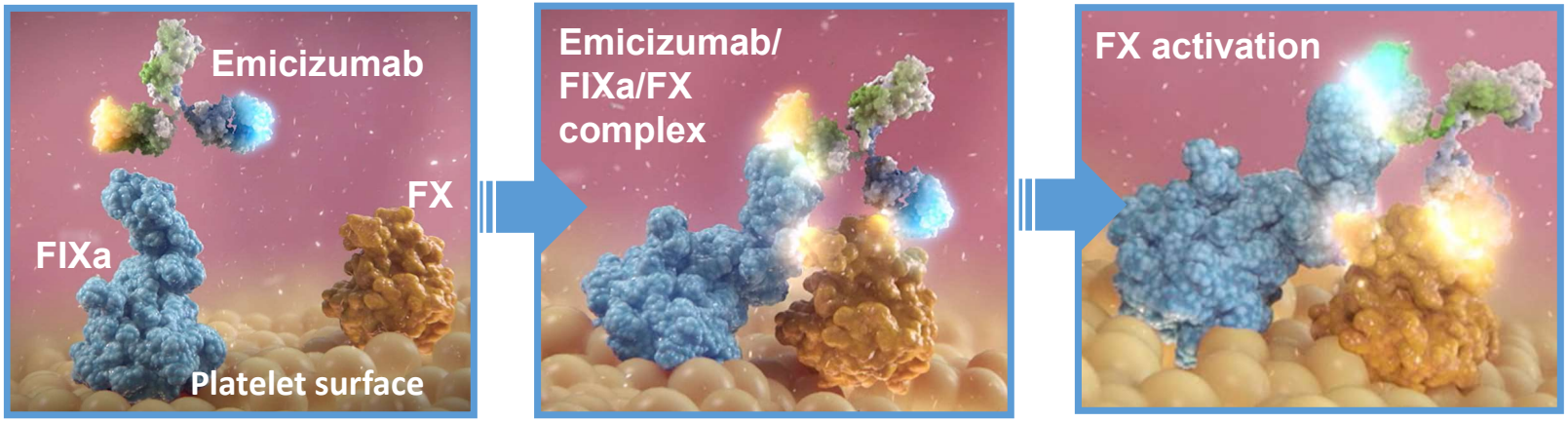
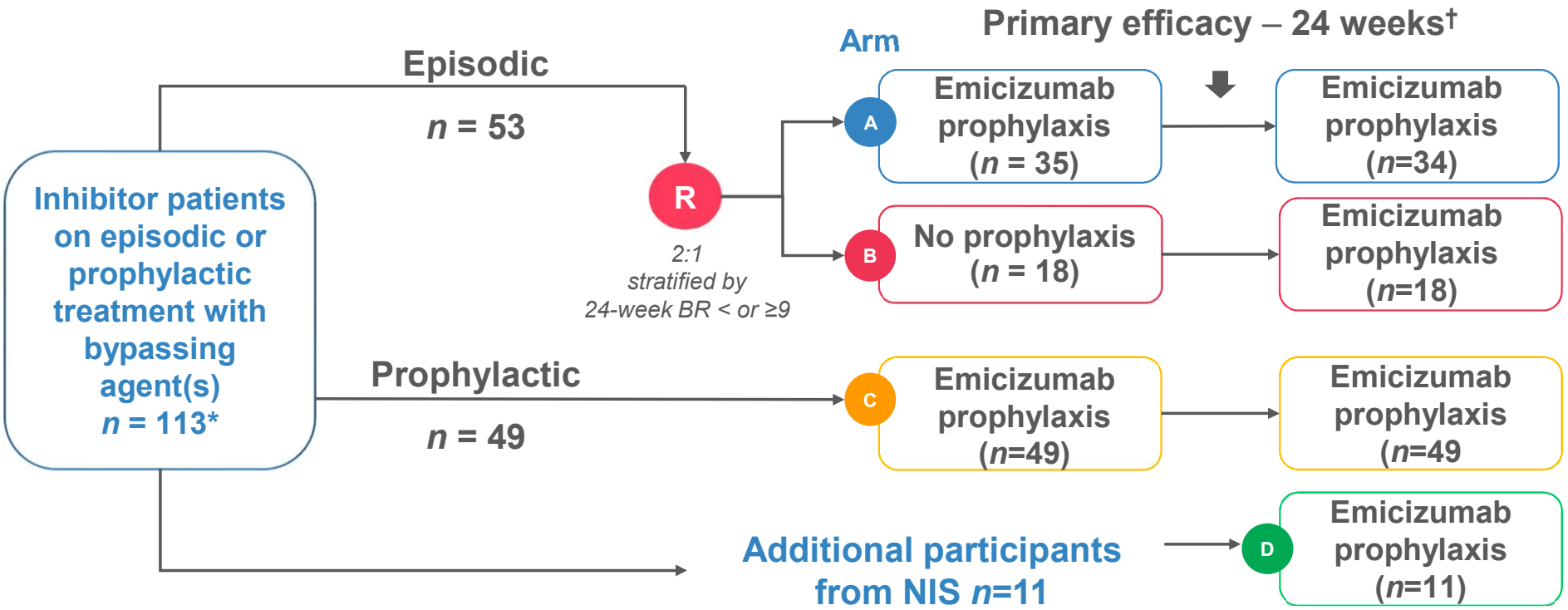
Emicizumab: mecanismo de acción



- Al ser un anticuerpo monoclonal biespecífico, emicizumab remplaza la función hemostática del FVII a través de la unión al FIXa y al FX.
- De este modo se permite que la cascada de la coagulación continúe de un modo similar a las condiciones normales.
- Los inhibidores frente al FVIII no se fijan o neutralizan a emicizumab, no teniendo ningún impacto en su actividad hemostática.

HAVEN 1: diseño del estudio

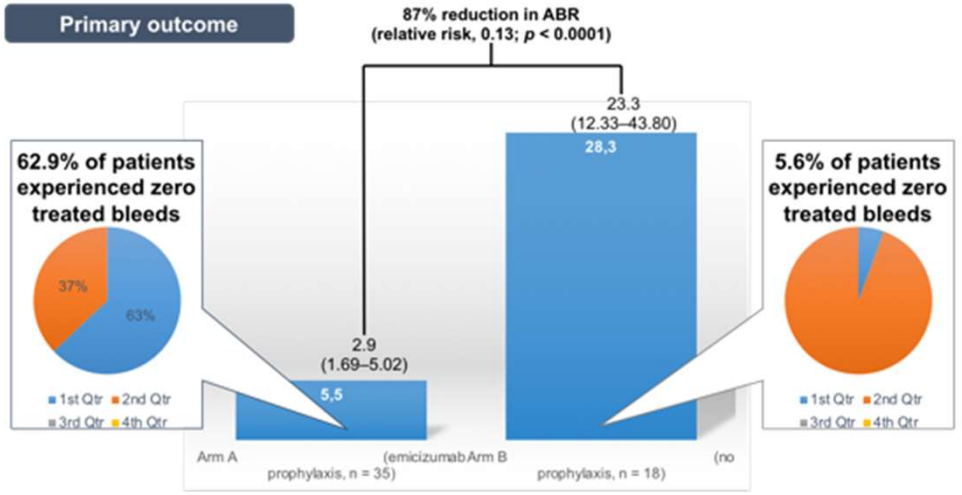


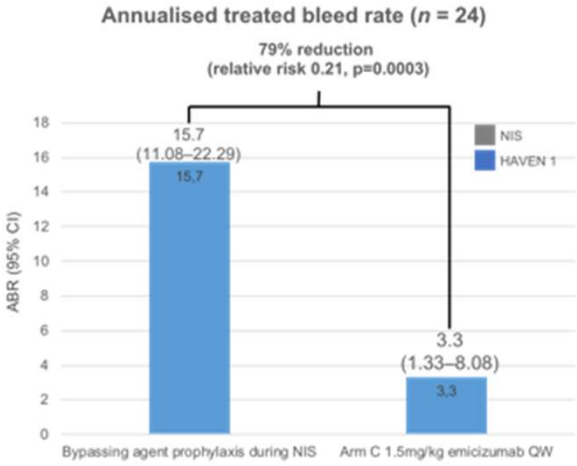
NB, episodic bypassing agent(s) could be used in all treatment arms to manage breakthrough bleeds
*Includes 70 patients from NIS, allowing intra-individual comparison in Arms A and C
†When last patient completes 24 weeks on-study or discontinues study participation, whichever occurs first
‡Option to increase dose in emicizumab arms if suboptimal response or rollover from control to emicizumab arm
BR, bleeding rate; NIS, non-interventional study; R, randomised

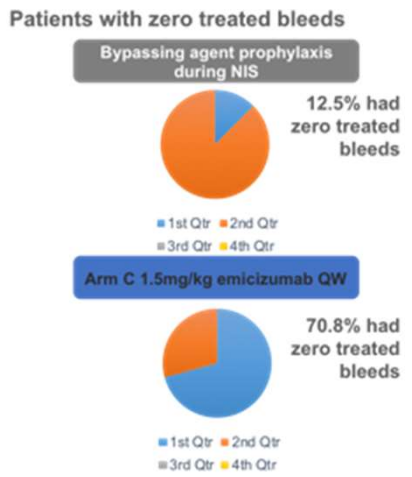
Mancuso ME et al. ASH 2017; poster 1071

HAVEN 1

- Primary analysis*,[1]:
  - ABR was reduced by **87%** (P<0.001) with emicizumab prophylaxis vs no prophylaxis†
  - The majority of patients on emicizumab prophylaxis had zero treated bleeds:
    - **62.9%** with emicizumab prophylaxis
    - **5.6%** with no prophylaxis
  - ABR was significantly reduced with emicizumab prophylaxis vs prior BPA use‡
    - By **92%** vs prior episodic BPAs (P<0.001)
    - By **79%** vs prior prophylactic BPAs (P<0.001)

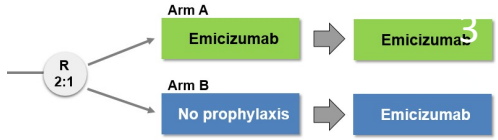


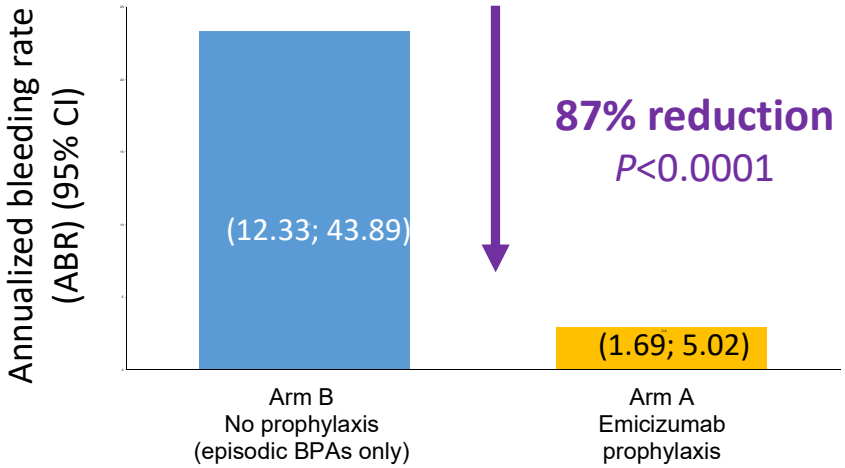


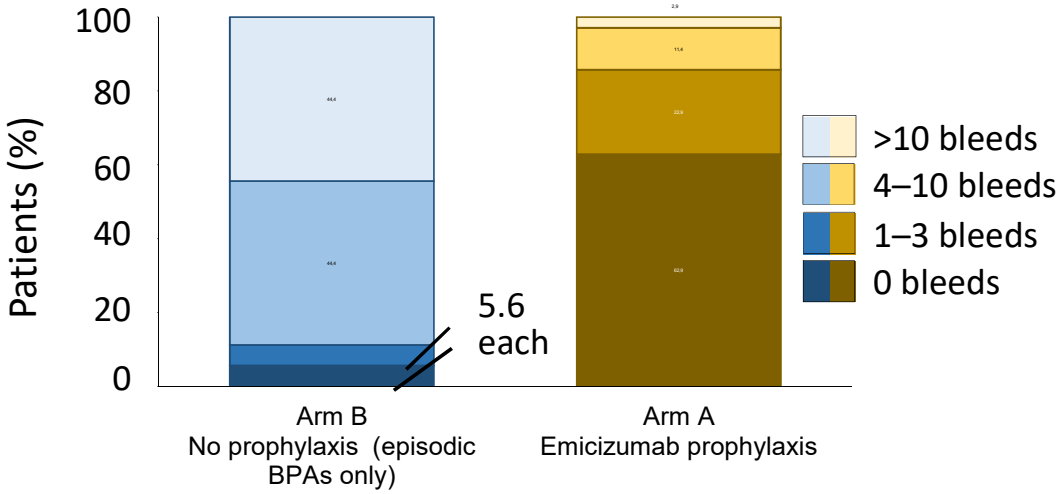


*Data cutoff: 25 October 2016. †Only episodic BPAs allowed. ‡Among patients who previously participated in a prospective non-interventional study (NCT02476942)..
ABR, annualised bleeding rate; BPA, bypassing agent; PwHA, persons with haemophilia A.
1. Oldenburg J, et al. *N Engl J Med* 2017;377:809–18.

HAVEN 1 endpoint primario
Comparación de los sangrados tratados







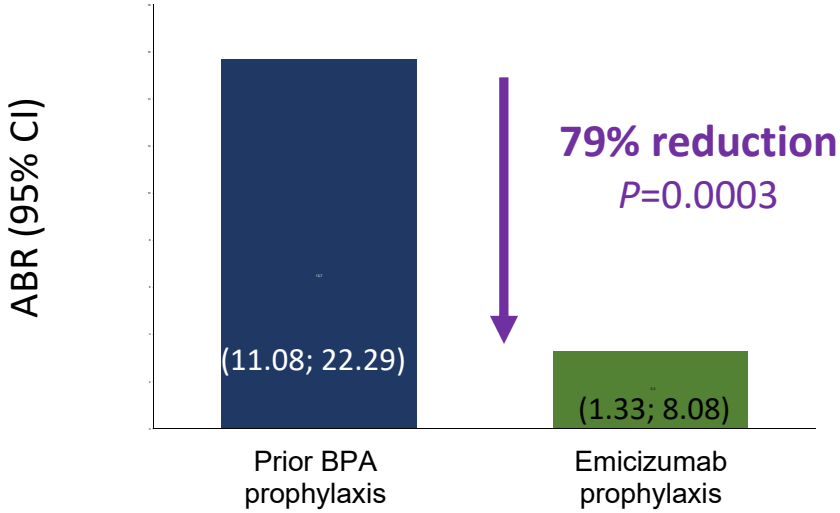
Median ABR (IQR)	18.8 (12.97; 35.08)	0.0 (0.00; 3.73)

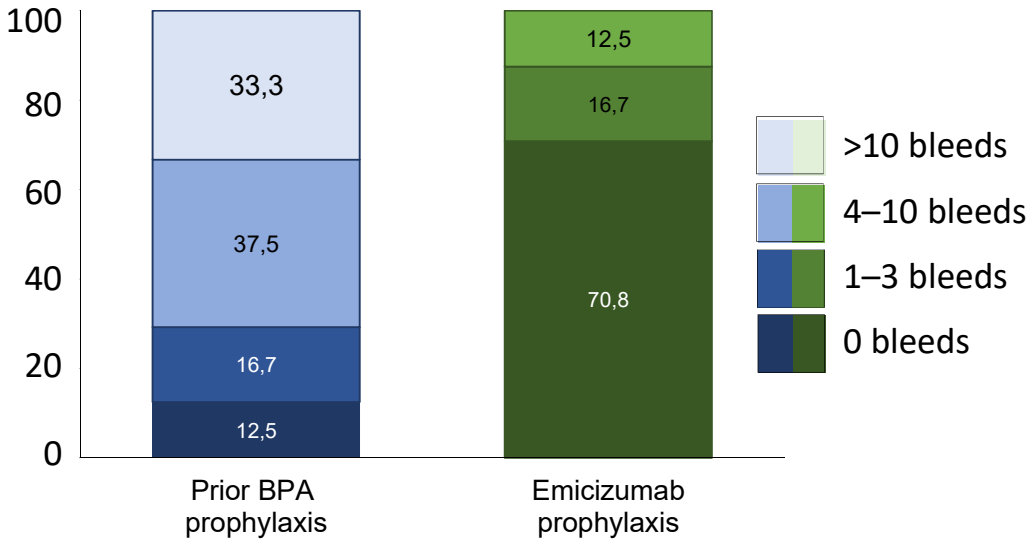
- Statistically significant, clinically meaningful reduction in bleed rate with emicizumab
- 62.9% of patients experienced zero bleeds with emicizumab prophylaxis
- To date, no patients have discontinued due to lack of efficacy

ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.
CI, confidence interval; IQR, interquartile range.

Primary analysis data cutoff – October 25, 2016

Comparación intra-individual : sangrados tratados con profilaxis con emicizumab vs profilaxis previa con agentes BP





Median ABR (IQR)	**12.0** **(5.73; 24.22)**	**0.0** **(0.00; 2.23)**

- Statistically significant, clinically meaningful reduction in bleed rates with emicizumab prophylaxis vs prior BPA prophylaxis
- 71% of patients with zero bleeds on emicizumab prophylaxis

ABR calculated with negative binomial regression model.
Median ABR calculated by number of bleeds/duration of efficacy period in days*365.25.

HAVEN 1: seguridad

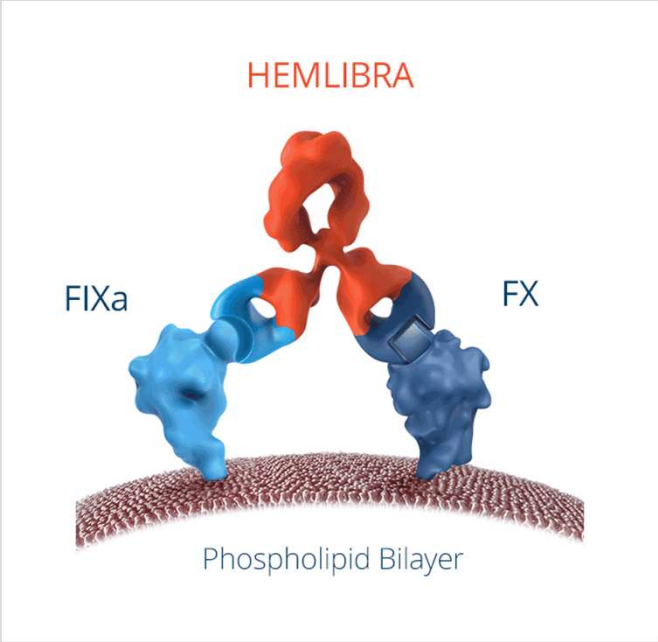
	Total (*N* = 112)
Number of AEs, *n*	457
Patients with ≥1 AE, *n* (%)	96 (85.7)
SAE	19 (17.0)
TMA	3 (2.7)
Thrombotic event	2 (1.8)
Death*	1 (0.9)
AEs leading to withdrawal	3 (2.7)
Grade ≥3 AE	14 (12.5)
Treatment-related AE	32 (28.6)
Local injection-site reaction	16 (14.3)

Since the provision of guidance on use of BPAs, no further patients have had TMA or other serious thrombotic events

*related to an AE

Menicucci ME et al. ASH 2017; poster 1071

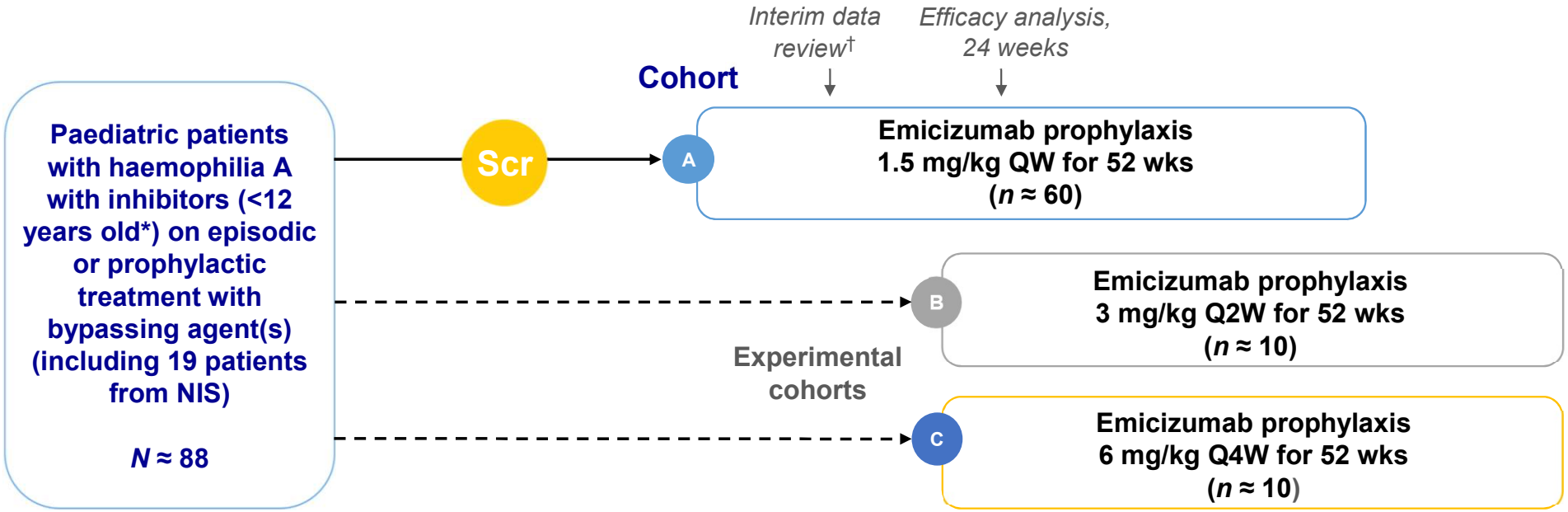
HEMLIBRA



EMICIZUMAB HA SIDO APROVADO:

- ✓ FDA Noviembre 2017: profilaxis en pacientes adultos/pediátricos con hemofilia A con inhibidor
- ✓ EMA Enero 2018: pacientes con hemofilia A con inhibidor
- ✓ FDA Octubre 2018: pacientes con hemofilia A sin inhibidor

HAVEN 2 study design

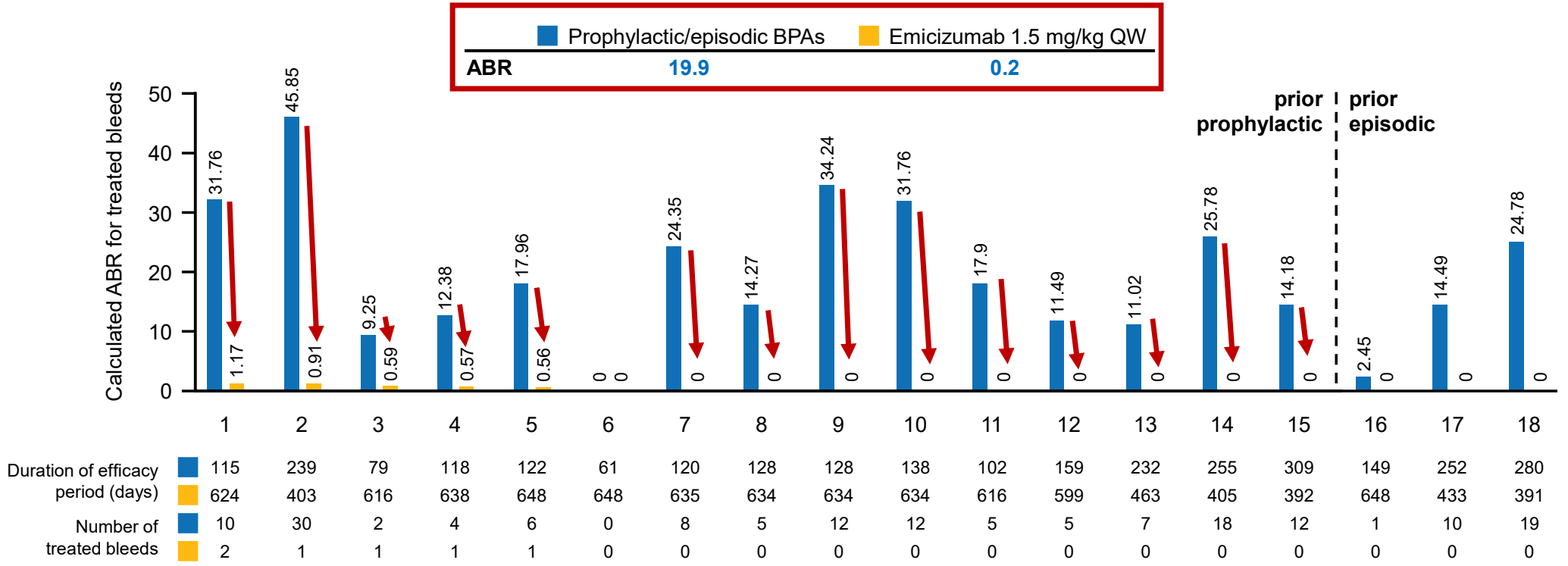


Loading dose of 3 mg/kg/week for 4 weeks in all cohorts; maintenance dose starting Week 5

*With allowance of patients 12–17 years old who weigh <40 kg. No patients <2 years old or 12–17 years old can enrol in Q2W or Q4W cohorts.
†For evaluation of starting dose (first 20 patients) and determination of whether dose modification is needed
‡Paediatric dosing regimen selected to target a similar C_{trough} to adult population with uncertainty of maintenance dose due to potential effects of body weight and clearance maturation
NIS, non-interventional study; Scr, screened; QW, once-weekly administration; Q2W, administration every 2 weeks; Q4W, administration every 4 weeks

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02795767 [Accessed 4 July 2017]
Bi-monthly emicizumab update: data on file

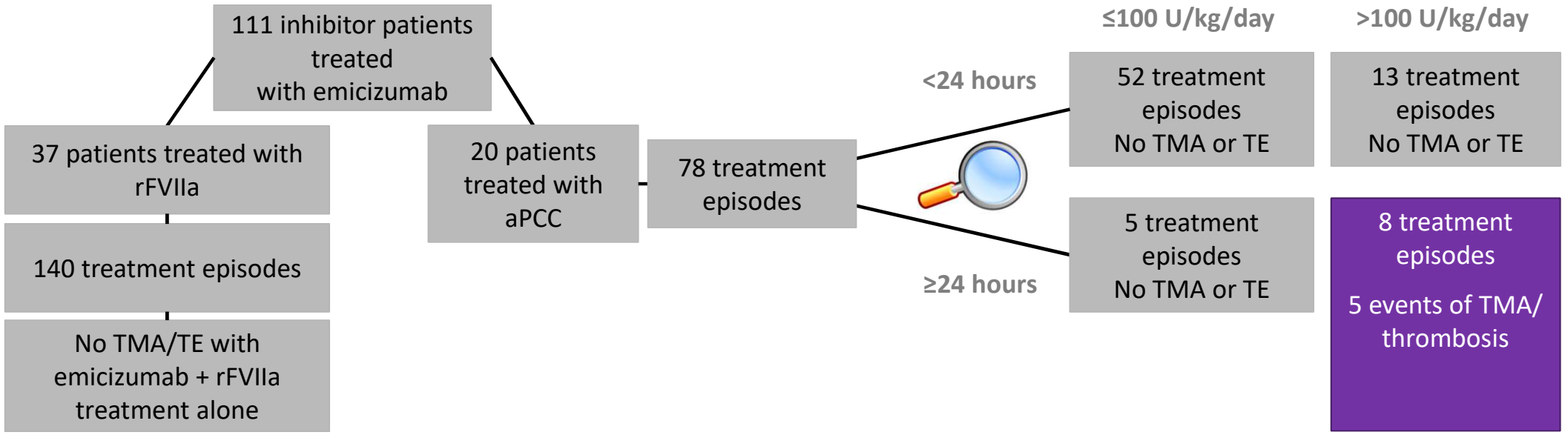
Reduced risk of treated bleeds with emicizumab vs prior BPA treatment



- Intra-individual comparison of 18 participants who had participated in the NIS showed a **99% (95% CI, 97.7–99.4) reduced risk** of treated bleeds with emicizumab compared with prior BPA treatment (ABR: 0.2 vs 19.9, respectively)

Intra-individual comparison includes 18 of 19 participants previously enrolled in the NIS <12 years old

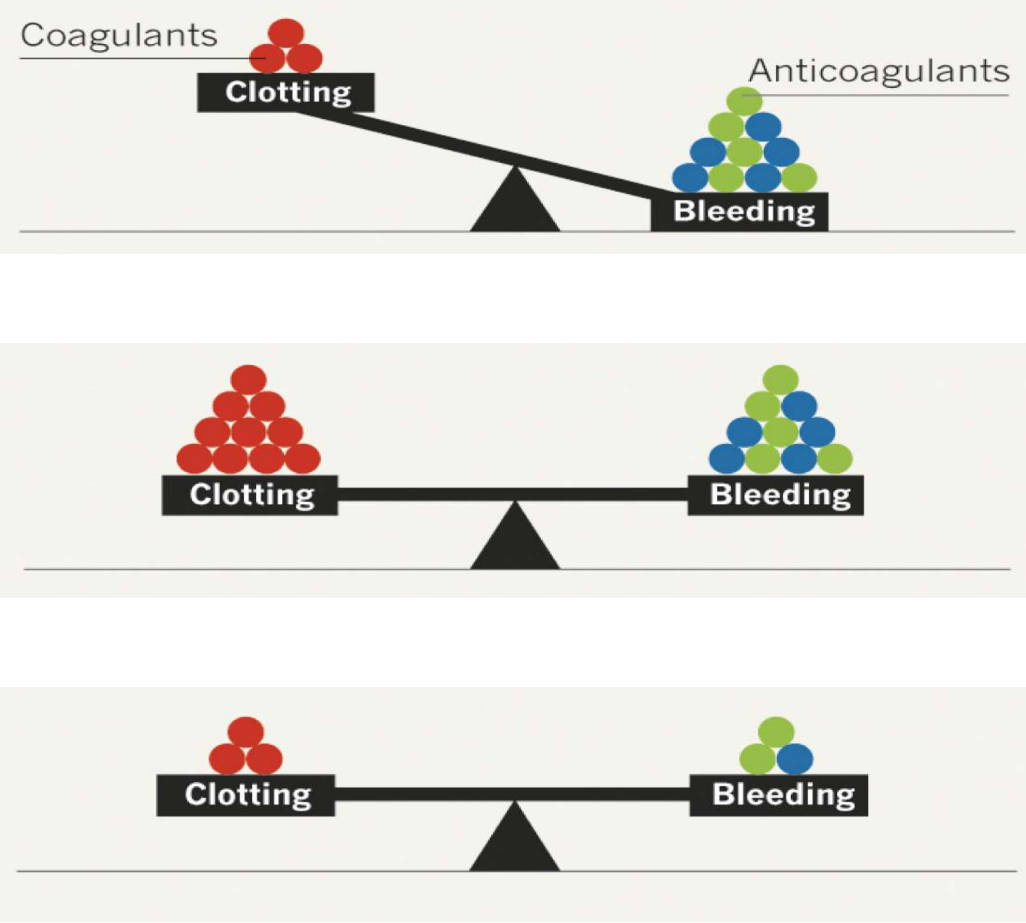
Analysis of safety events in HAVEN 1



TMA/thrombotic events only occurred with aPCC treatment averaging >100 U/kg daily for ≥24 hours

No further SAEs of TE/TMA in >350 patients treated in emicizumab development programme to date

Una visión diferente



Concizumab: EXPLORER™ 3

journal of thrombosis and haemostasis™

ISTH International Society on Thrombosis and Haemostasis

Original Article - Coagulation

Safety, pharmacokinetics and pharmacodynamics of concizumab in people with hemophilia A: a phase 1b, randomized trial

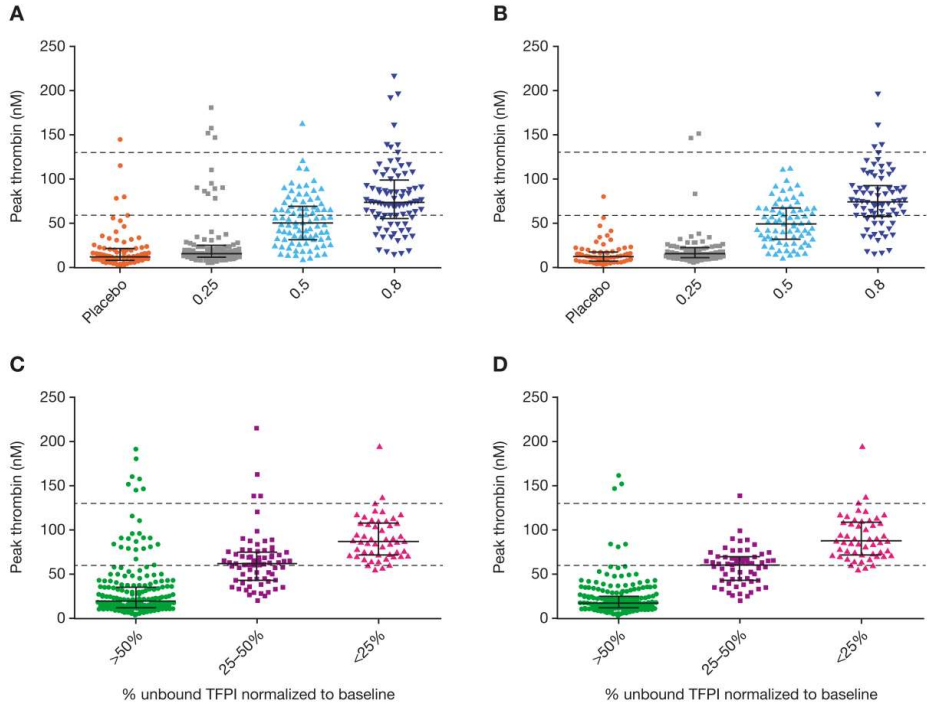
Hermann Eichler ✉, Pantep Angchaisuksiri, Kaan Kavakli, Paul Knoebl, Jerzy Windyga, Victor Jiménez-Yuste, Agon Hyseni, Ute Friedrich, Pratima Chowdary

First published: 23 August 2018 | https://doi.org/10.1111/jth.14272

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jth.14272

Concizumab: EXPLORER™ 3

- explorer™3 was a double-blinded, multiple-dose escalation trial of subcutaneous concizumab.
- A pharmacodynamic relationship for unbound TFPI and thrombin generation was confirmed.
- No serious adverse events and no anti-drug antibodies were observed.
- explorer™3 data support further clinical development of concizumab in people with hemophilia.



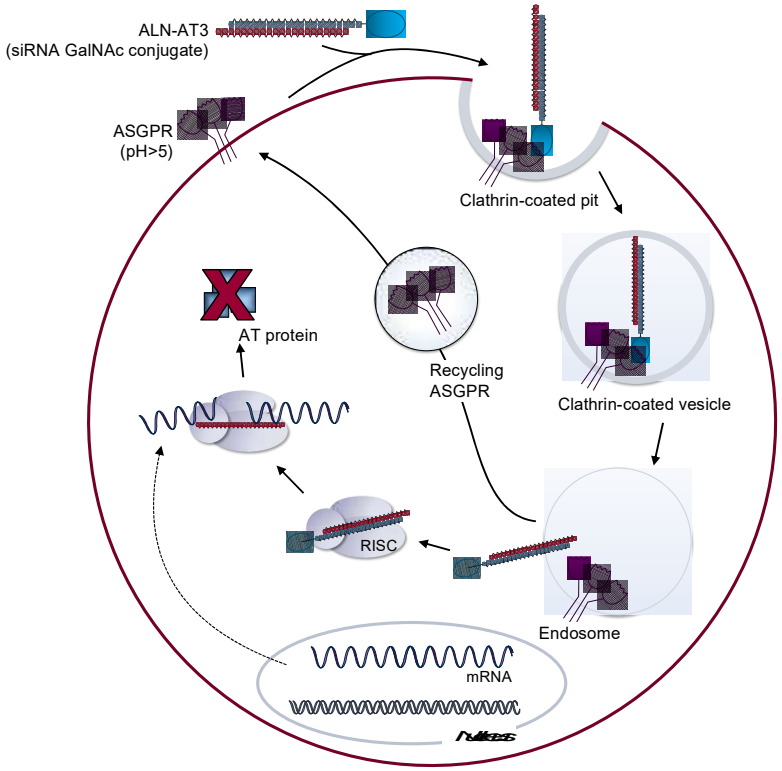
Correlation between concizumab and peak thrombin generation potential by dose cohort (A) including and (B) excluding values within 72 hours after dosing with FVIII concentrate, as well as correlation between unbound TFPI and peak thrombin generation potential (C) including and (D) excluding values within 72 h after dosing with FVIII concentrate

Concizumab: EXPLORER™ 3

- The treatment duration in explorer™3 (42 days) allowed a preliminary assessment of the ability of concizumab to prevent bleeding episodes.

- Although the study was not designed or powered to assess efficacy, a trend towards lower bleeding rates was observed in patients in the highest concizumab dose cohort (0.8 mg/kg), seen as increased differences between on treatment versus pre- and post-treatment bleeding rates compared with the lower dose cohorts.

ALN-AT3: Fitusiran



- RNAi (RNA interference) is a natural process of gene silencing that occurs in organisms ranging from plants to mammals.
- A short interfering RNA (siRNA), ALN-AT3, employing a hepatocyte targeting ligand has been developed against AT
- AT acts as an important endogenous anticoagulant by inactivating FXa and thrombin

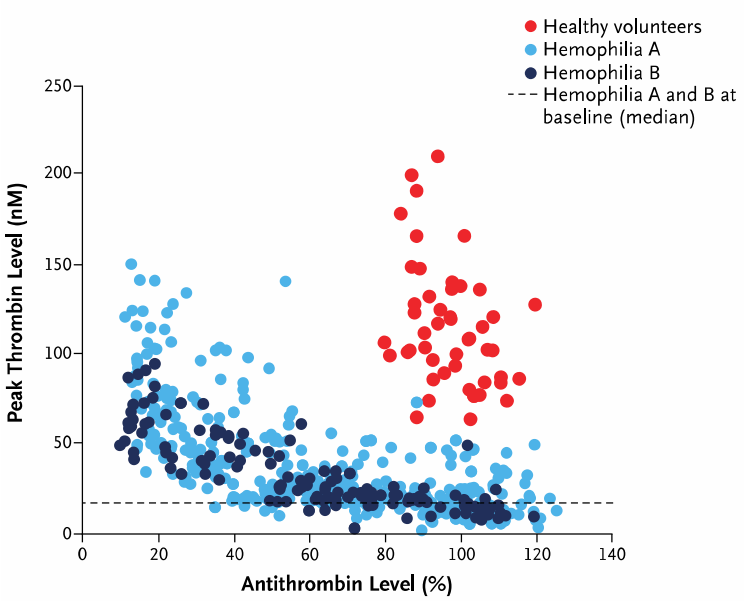
Fitusiran reduces antithrombin production

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy

K.J. Pasi, S. Rangarajan, P. Georgiev, T. Mant, M.D. Creagh, T. Lissitchkov, D. Bevan, S. Austin, C.R. Hay, I. Hegemann, R. Kazmi, P. Chowdary, L. Gercheva-Kyuchukova, V. Mamonov, M. Timofeeva, C.-H. Soh, P. Garg, A. Vaishnaw, A. Akinc, B. Sørensen, and M.V. Ragni

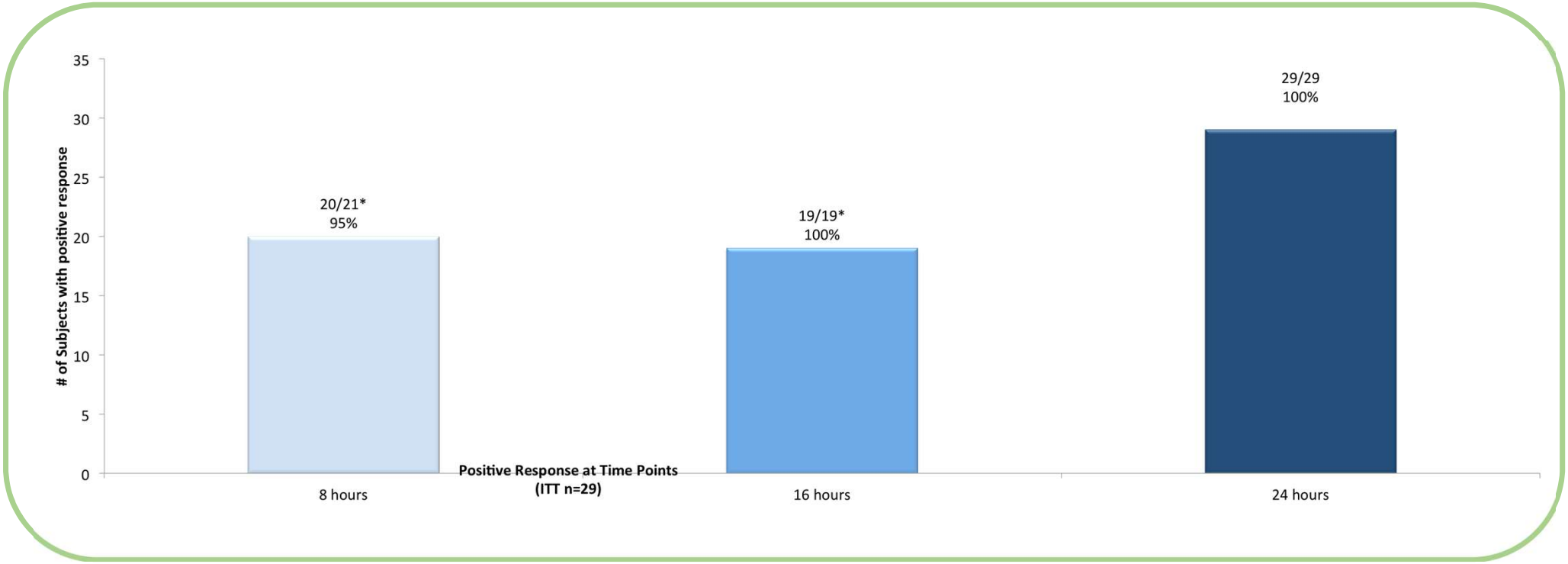


FVIIIr porcino (OBI-1): Obizur

- B-domain deleted recombinant porcine FVIII (rpFVIII)
- OBI-1 is a FVIII replacement therapy, not a bypass agent
- Sufficiently similar to human FVIII to cause haemostasis, but sufficiently different to be less cross-reactive with anti-human FVIII antibodies
- Ability to monitor FVIII levels provides an objective surrogate measure of haemostatic efficacy and safety

Kempton, C *et al. Haemophilia* 2012:18:798-804

FVIIIr porcino (OBI-1): Obizur



100% of treated subjects showed a positive response at 24 hours

25 effective / 4 partially effective

Kruse-Jarres R et al. Oral presentation. WFH 2014

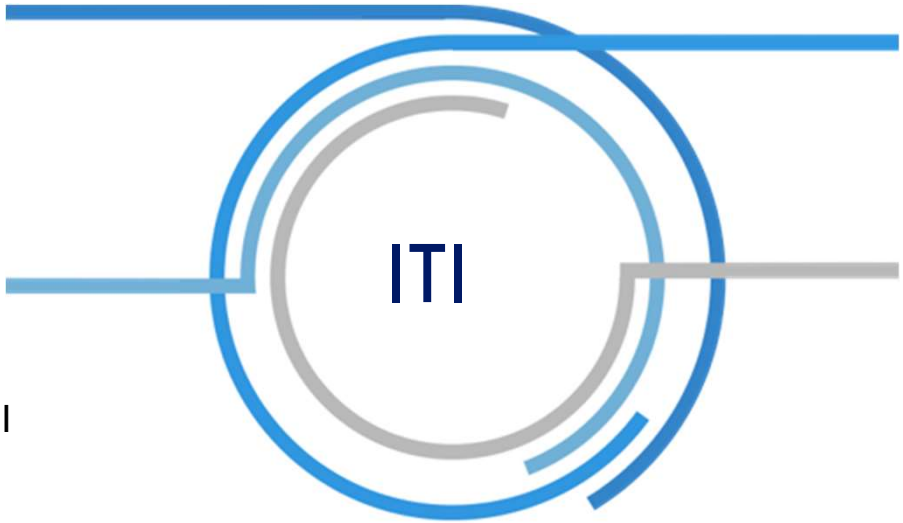
Estrategias Inmunotolerancia

EPISODIOS HEMORRÁGICOS

INMUNOTOLERANCIA

ITI

El único método probado en la erradicación de los inhibidores es la inducción a la inmunotolerancia (ITI).

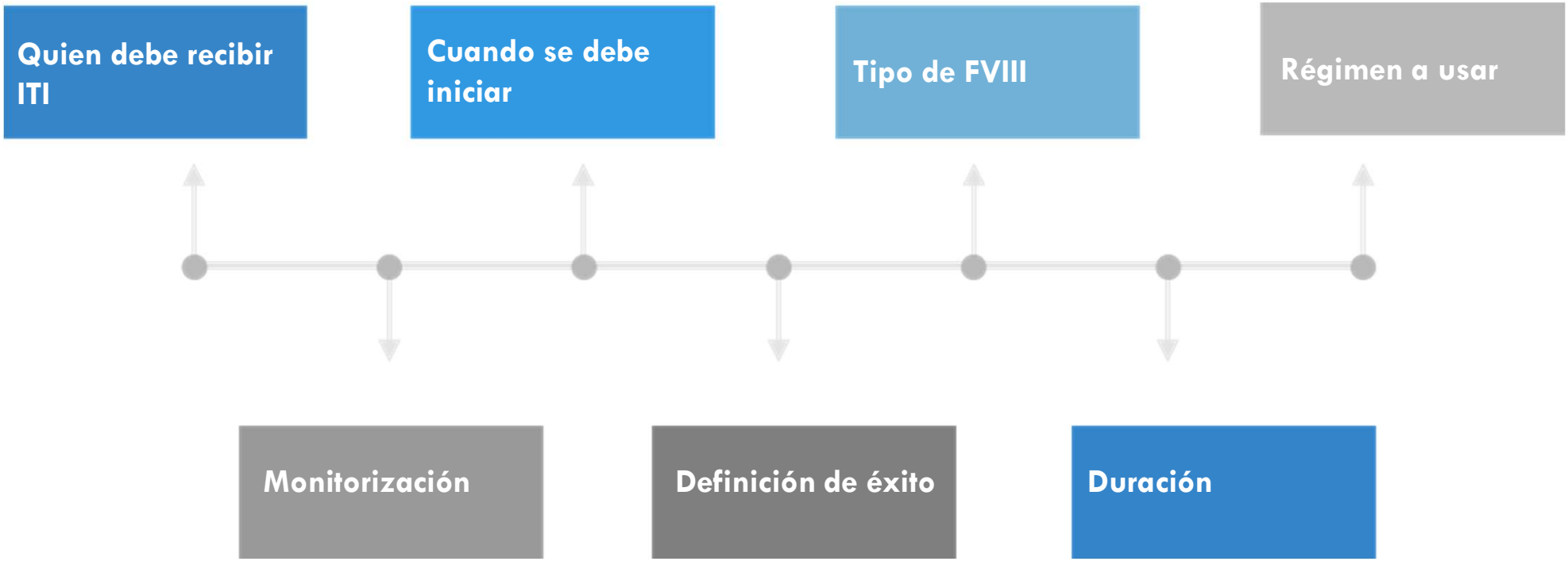


ITI es la infusión regular de FVIII para inducir tolerancia de FVIII antígeno-específica.

La tasas de eficacia varían aproximadamente entre 60 al 80%.

La mayor desventaja es su elevado coste inicial

Cuestiones abiertas



- 1.Valentino LA et al. Haemophilia 2015; Sep;21(5):559-67,

Descripción original de Bonn: ALTAS DOSIS

MASSIVE FACTOR-VIII INFUSION IN HÆMOPHILIAC WITH FACTOR-VIII INHIBITOR, HIGH RESPONDER

SIR,—Bleeding in hæmophiliacs with factor-VIII inhibitors of low-responder type is generally overcome by massive factor-VIII infusions.[1] The addition of immunosuppressive therapy may be successful in high responders, delaying and possibly weakening the anamnestic response.[2,3] "Activated" factor-IX concentrates may also be useful.[4] These regimens, however, are unsuitable when prolonged substitution therapy is necessary in a high responder.

Our patient is a 20-year-old hæmophiliac with factor-VIII inhibitor. His elder brother, also a hæmophiliac with inhibitor, died aged 18 from a retroperitoneal hæmorrhage. Our patient has had bleeding episodes since birth and has been given many infusions of whole blood, plasma, cryoprecipitate, and factor-VIII concentrates in more than thirty hospital admissions, without much success. Inhibitor was detected when he was 12 years old. Three times he has received concentrates in combination with immunosuppressive therapy, the last (1973) being with cyclophosphamide (15 mg/kg intravenously followed by 2 mg/kg body-weight orally for 10 days) when the inhibitor concentration increased after 4–5 days from 0·5 units/ml to a peak of 30–40 units/ml after 2 weeks. The preinfusion level was regained after 2 months. In 1976 at the age of 18 he passed his final school examination, brilliantly, but he was confined to a wheelchair or bed and he wanted to be more independent. This would need prolonged physiotherapy, which could be achieved only if covered by factor-VIII after elimination of inhibitor. We decided to use the treatment given by the hæmophilic centre in Bonn[5]—a combination of daily massive infusions of factor VIII and activated factor IX until the increase in inhibitor, which follows infusions, has been eliminated, after which daily doses should keep the inhibitor level low and permit physiotherapy. Our patient was treated in Bonn. His factor-VIII level was 1% and his inhibitor level was 0·5 Bethesda units/ml on admission. The dosages and inhibitor levels are shown in the figure. At first he received 3000 units of factor VIII and 2500 units of concentrated factor IX daily. His inhibitor level increased during the first week to about 1100 units/ml and did not fall significantly until he had received 12 000 units of factor VIII per day for 10 days. The dose could then be reduced, and after 3 months with daily injections an inhibitor level of 1 unit/ml was obtained. The inhibitor concentration rose 3 weeks later, the daily dosage of factor VIII having been reduced too far, but the inhibitor concentration fell again when the dose was increased. After 7 months he has no demonstrable inhibitor while on 3000 units of factor VIII and 1000 units of factor IX concentrate ('Feiba') daily. He received, due to shortage of feiba, other factor-IX concentrates in between.

There have been a few bleeding episodes, mostly in one bad elbow but sometimes more general. In more general bleeds we often found a positive ethanol test, increased amounts of fibrinogen-related antigens, shortened euglobulin-lysis time, a low platelet-count, and a defect in A.D.P., adrenaline, and collagen-induced platelet aggregation in vitro. He has biochemically no hepatic or renal damage. Platelet or leucocyte antibodies and hepatitis B antigen or antibody have not been found. He has been able to do progressively more active physiotherapy, and is making great progress. Furthermore he has passed another examination, and is able to use his typewriter again. Except for the first days in Bonn he has administered the injections himself.

A feature of this case is the very high level of inhibitor and the very large doses of factor VIII.

1. Albin, J. P., Frommel, D. *Rev. Fr. Etud. Clin. Biol.* 1976, **47**, 957.
2. Dormandy, K., Hockey, C., Churchill, W. G. J., Cowley, J. *Thromb. Diath. Haemorrh.* 1971, **43**, 355.
3. Nielsen, J. M., Hedner, U. *Scand. J. Haematol.* 1976, **16**, 364.
4. Mannucci, P. M., Bader, R., Ruggeri, Z. M. *Lancet* 1976, i, 41.
5. Brackmann, H. H., Bürzl, F., Hofmann, P., Egli, H. *Thromb. Haemostas.* 1977, **38**, 369 (abstr.).

Institute of Experimental Hematology and Blood Transfusion, University of Bonn, Bonn, West Germany
H. H. BRACKMANN

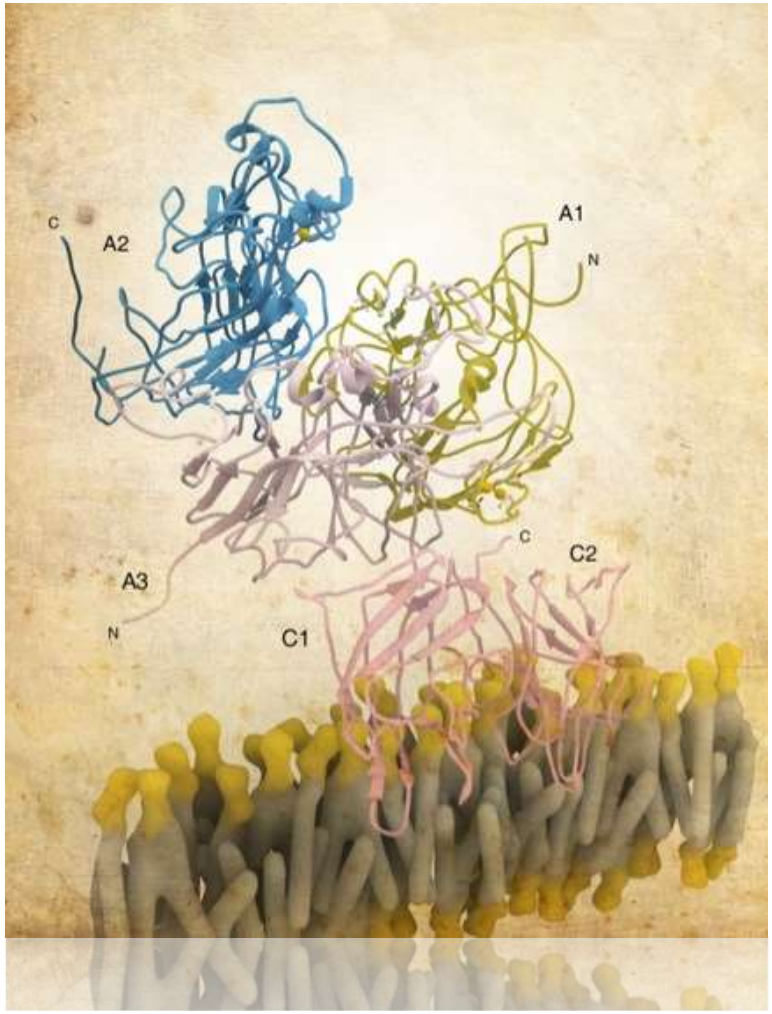
Coagulation Laboratory, Municipal Hospital, 1399 Copenhagen K, Denmark
J. GORMSEN

- FASE I:
  - 100 UI FVIII/12h
  - 50 U FEIBA®/12h
  - Hasta inhibidor < 1UB
- FASE II
  - 100 UI FVIII/12h
  - Hasta desaparición de inhibidor
- FASE III
  - 100 UI FVIII/24h
  - Hasta normalización de vida media
- FASE IV
  - Suspensión tratamiento: Demanda o profilaxis

Bonn protocol (high-dose regimen)
FVIII 100 IU/kg twice daily
FEIBA 50 IU/kg twice daily for patients at high risk of bleeding
van Creveld (Dutch) Protocol (low-dose regimen)
FVIII 25 IU/kg every other day (q.o.d)
Decrease dose each time absolute FVIII recovery is >30%
Continue until a prophylactic dose (10–15 IU/kg q.o.d.) is reached
Malmö Protocol (immunomodulation plus high-dose FVIII)
Immunoadsorption followed by
Immunosuppression with cyclophosphamide followed by IVIG replacement
FVIII
Other Protocols
Gruppo: 50–100 IU kg/week plus immunomodulation
Rocino: 100 IU kg/day
Smith: 100 IU/kg b.i.d., then 100 IU kg/day

Mecanismo ITI

- Mecanismo de ITI: no existe una explicación clara
- Desarrollo de anticuerpos antidiotipo
  - Sultan Y et al.. Proc Natl Acad Sci USA 1987; 84: 828–31.
  - Gilles JG et al. J Clin Invest 1996; 97: 1382–8.
- Pérdida de células B de memoria
  - Hausl C et al. Blood 2005; 106: 3415–22.
- Generación de células T reguladoras específicas FVIII
  - Miao CH et al. Blood 2009; 114: 4034–44.
  - Miao CH. Expert Rev Hematol 2010; 3: 469–83.



Factores predictores de éxito de ITI

Genéticos	Condiciones pre-ITI	Esquema terapéutico	Durante ITI
Genotipo FVIII	Título Pre-ITI	Dosis/frecuencia de FVIII	Pico inhibidor
Etnia	Título máximo histórico	Tipo de producto/FVW	Sangrado/cirugía
Inmunogenotipo	Edad inicio ITI		Procesos inflamatorios
	Tiempo entre diagnóstico - ITI		Interrupción ITI

Factores predictores de éxito de ITI

Genéticos	Condiciones pre-ITI	Esquema terapéutico	Durante ITI
Genotipo FVIII	Título Pre-ITI	Dosis/frecuencia de FVIII	Pico inhibidor
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Inmunogenotipo	Edad inicio ITI		Procesos inflamatorios
	Tiempo entre diagnóstico y ITI		Interrupción ITI

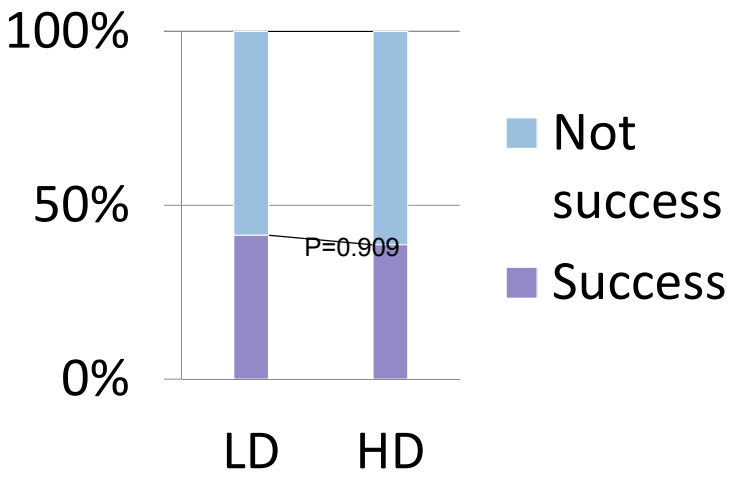
ITI study : dosis

- 2012. Hay CR and DiMichele D. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood 2012; 119 (6): 1335-44.

- Multicéntrico, prospectivo, aleatorizado de alta dosis (HD:200 IU/kg/d) vs bajas dosis (LD: 50 IU/kg 3 veces/semana).
- rFVIII: 90% de los pacientes
- 115 “good-risk”, hemofilia A con alto título de inhibidor
- 66 de 115 alcanzaron los “end points”.

ITI study : dosis

- No existían diferencias de éxito de ITI entre ambas ramas (24 of 58 LD vs 22/57 HD, P= 0.909).
- El tiempo hasta conseguir detección negativa del inhibidor *(P =0.027)*, recuperación normal *(P= 0.002)*, y tolerancia *(P =0.116, nonsignificant)* fueron más corto con altas dosis.
- El pico histórico *(P= 0.026)* y el título en la ITI *(P=0.002)* se correlacionaron de forma inversa con el éxito.
- Solo el pico en la ITI predecía el éxito en el análisis multivariante.
- Sujetos en BD sangraban más frecuentemente que los de AD *(odds ratio, 2.2; P=0.0019)*.
- Ni el sangrado ni la infección influían en el éxito de ITI.



“Británicos": dose tailoring ITI

bjh guideline

Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition)

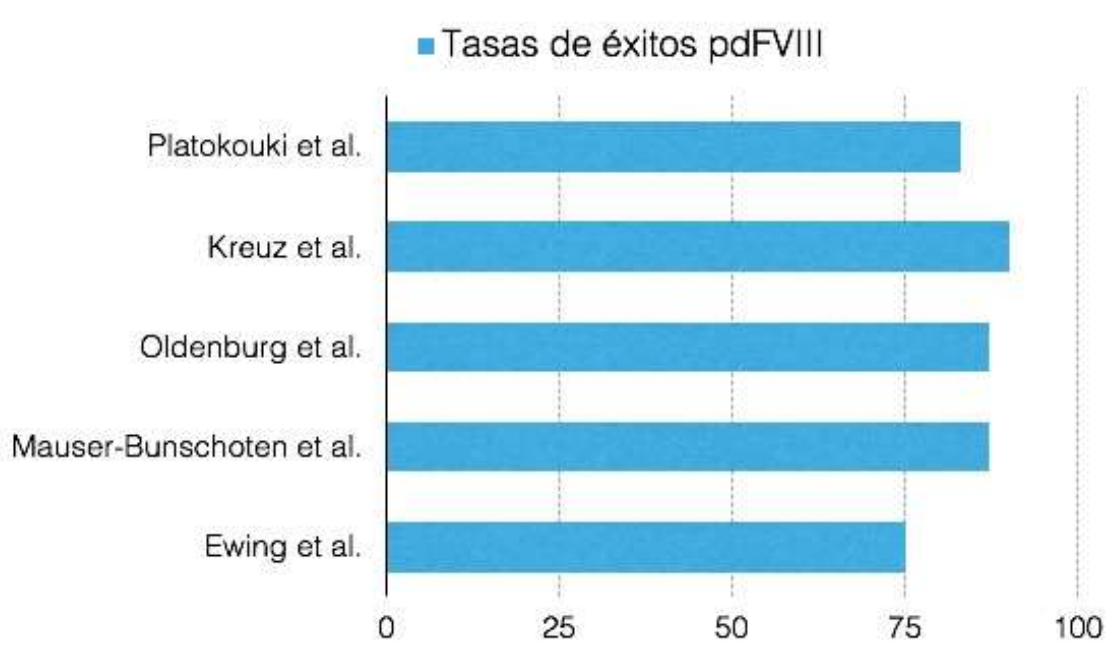
Peter W. Collins,[1] Elizabeth Chalmers,[2] Daniel P. Hart,[3] Ri Liesner,[4] Savita Rangarajan,[5] Kate Talks,[6] Mike Williams[7] and Charles R. Hay[8]

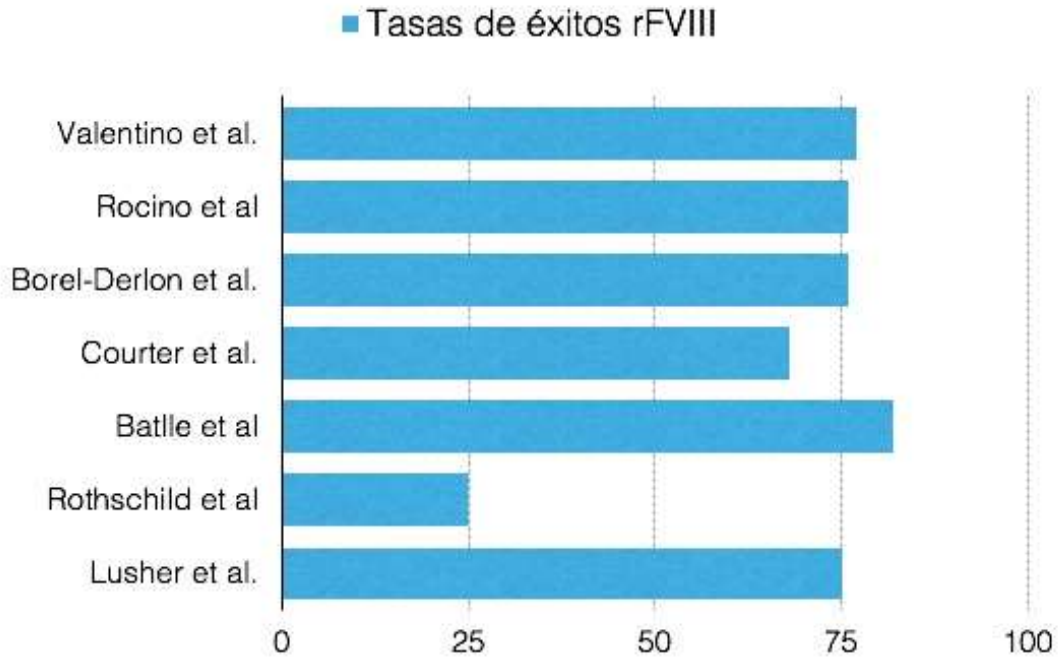
- DADO QUE el ITI-study…
  - 1. La dosis no parece influir en el éxito de pronóstico favorable
  - 2. AD se correlacionan solo con menor sangrado en fases iniciales de ITI
  - 3. Que el tiempo en obtener ITI solo es más corto hasta inhibidor negativo

ALTAS DOSIS

BAJAS DOSIS

ITI y tipo de producto





La solución