Hemofilia

Complicaciones del tratamiento : Inhibidores. Experiencia en la ITT con C. FVIII/FvW (®Fanhdi)

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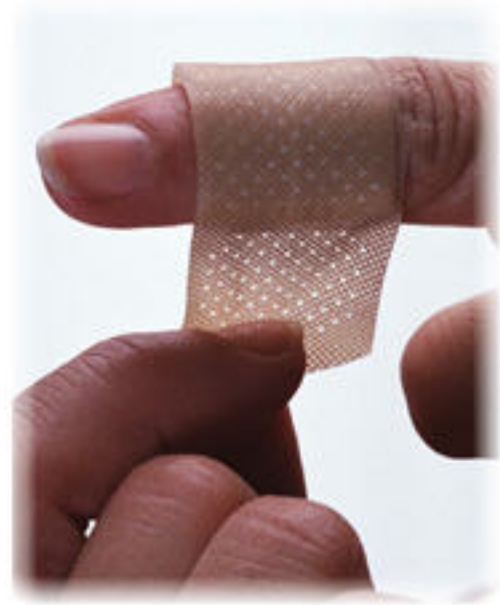
HEMOFILIAS

- Enfermedades hemorrágicas debidas a una deficiencia congénita:

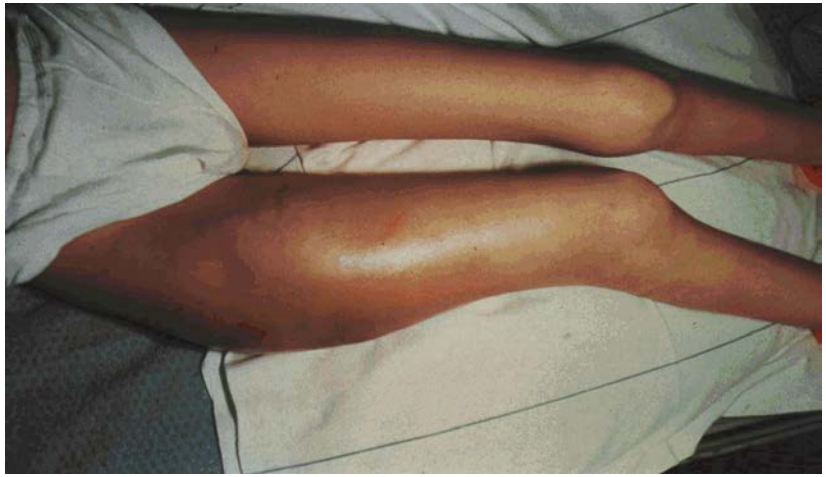
Factor VIII: (Hemofilia A)

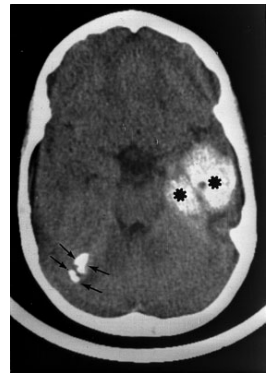
Factor IX: (Hemofilia B)

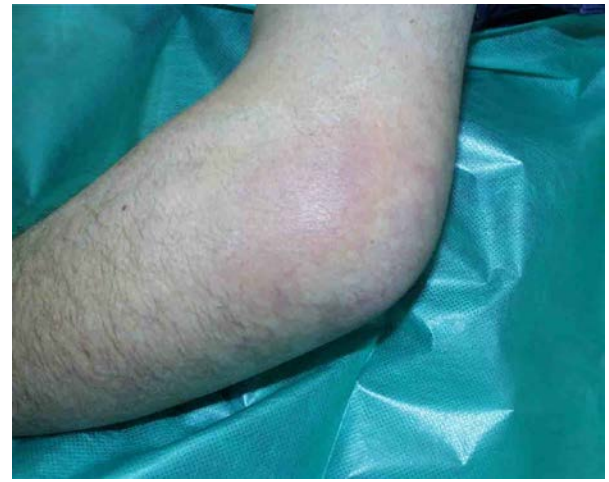


HEMOFILIAS

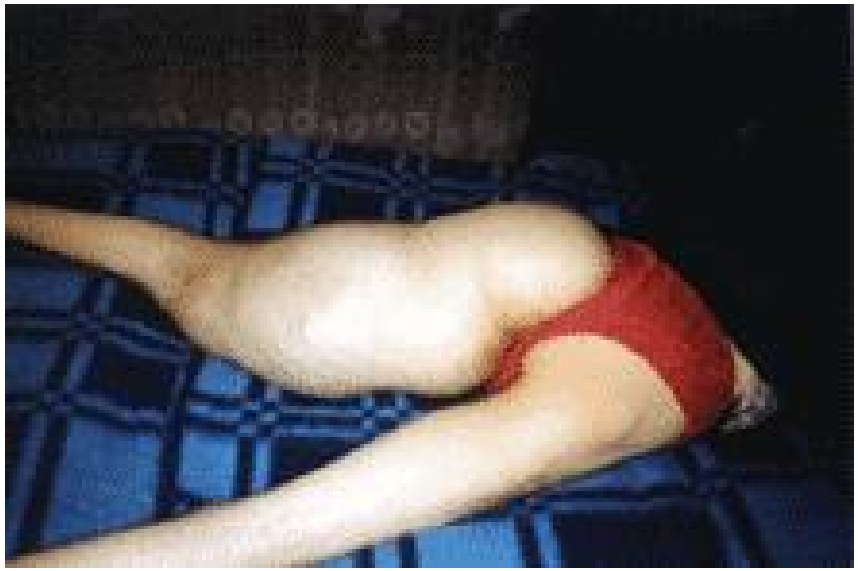
- El sangrado del paciente con hemofilia no es mas rápido que en otro paciente sin coagulopatía, pero si más duradero en el tiempo

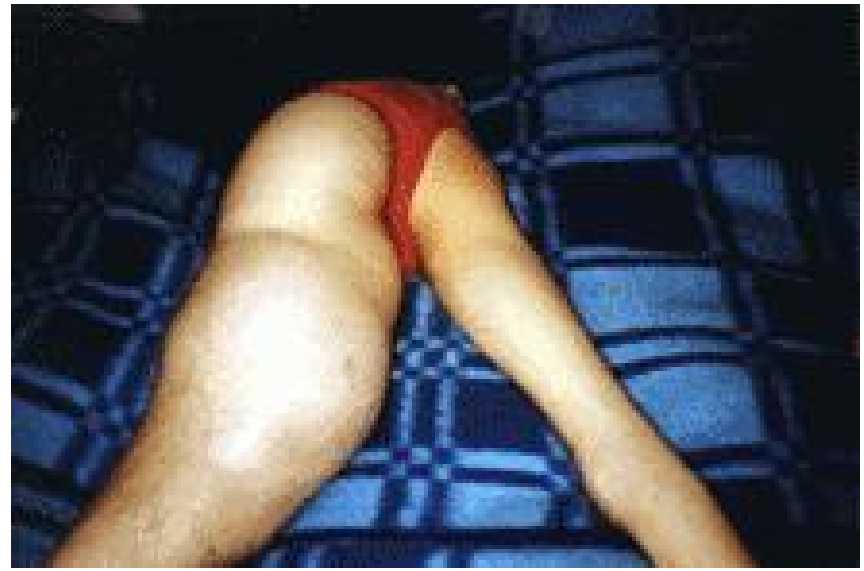






TRATAMIENTO: TERAPEUTICA SUSTITUTIVA





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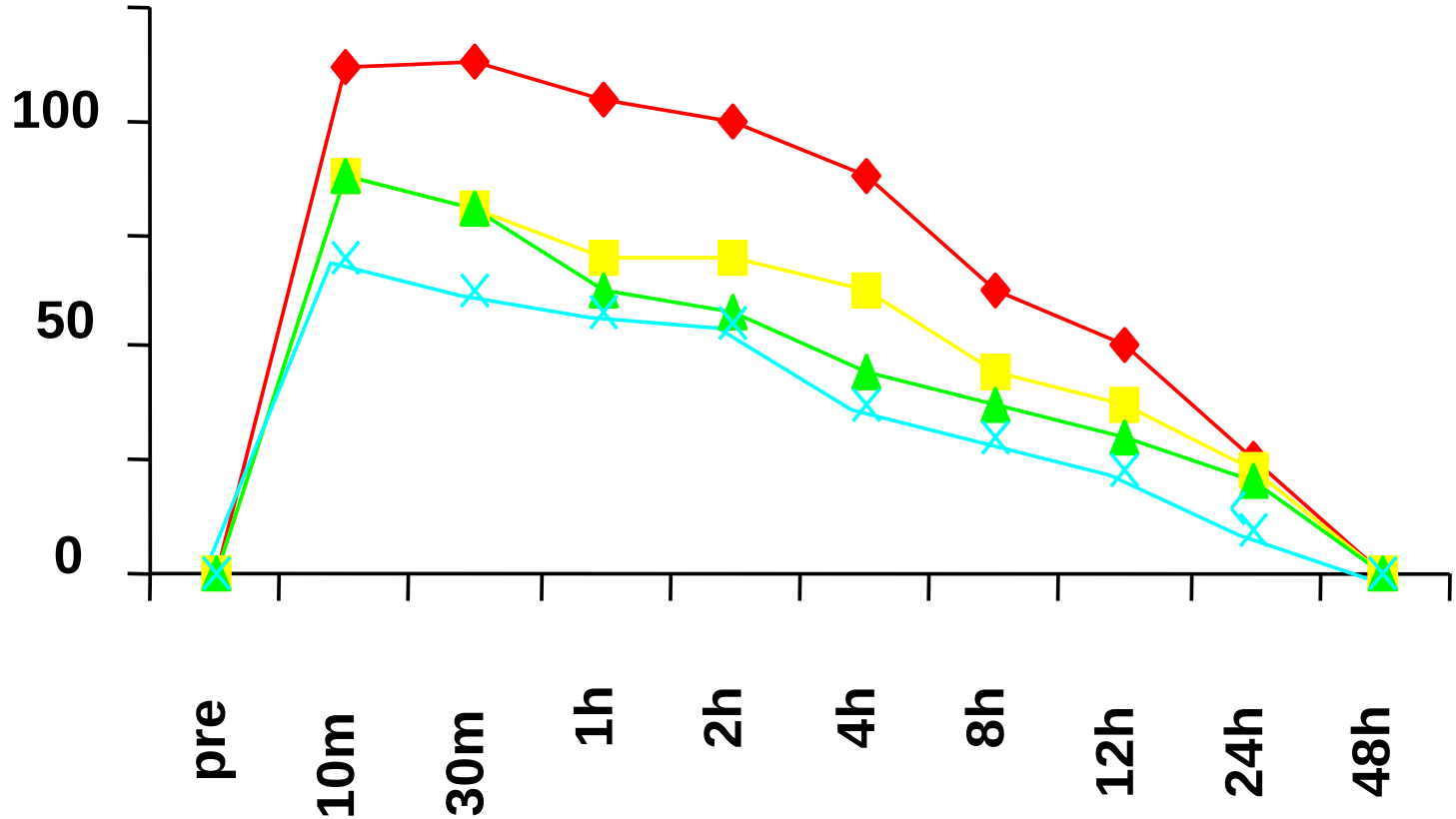
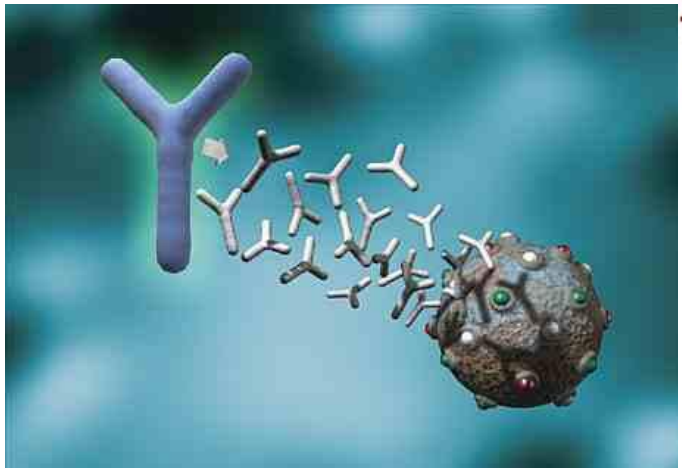
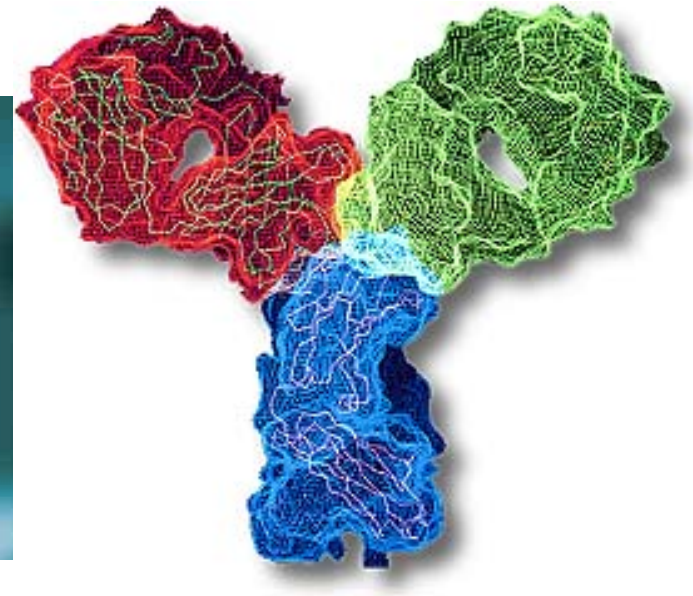
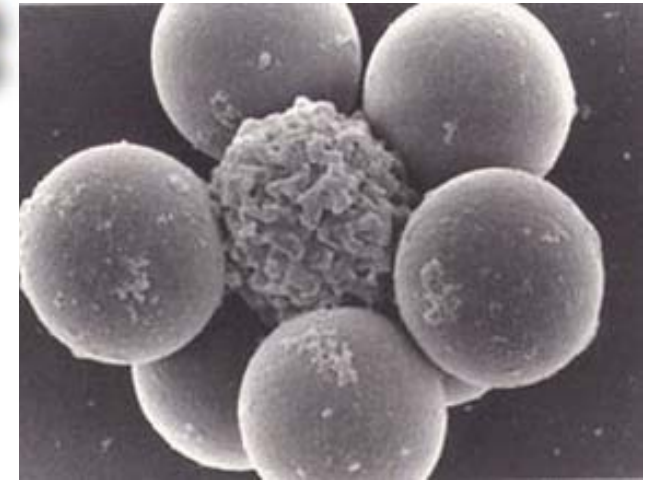


COMPLICACION DEL TRATAMIENTO

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

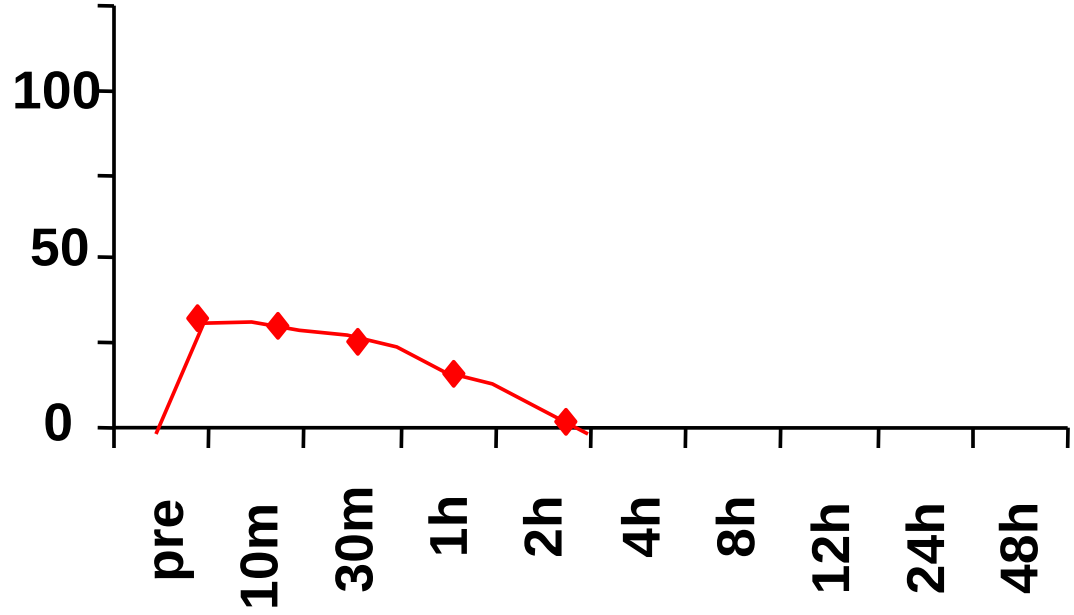






DESARROLLO DE INHIBIDORES

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



IMPORTANCIA DE LOS INHIBIDORES

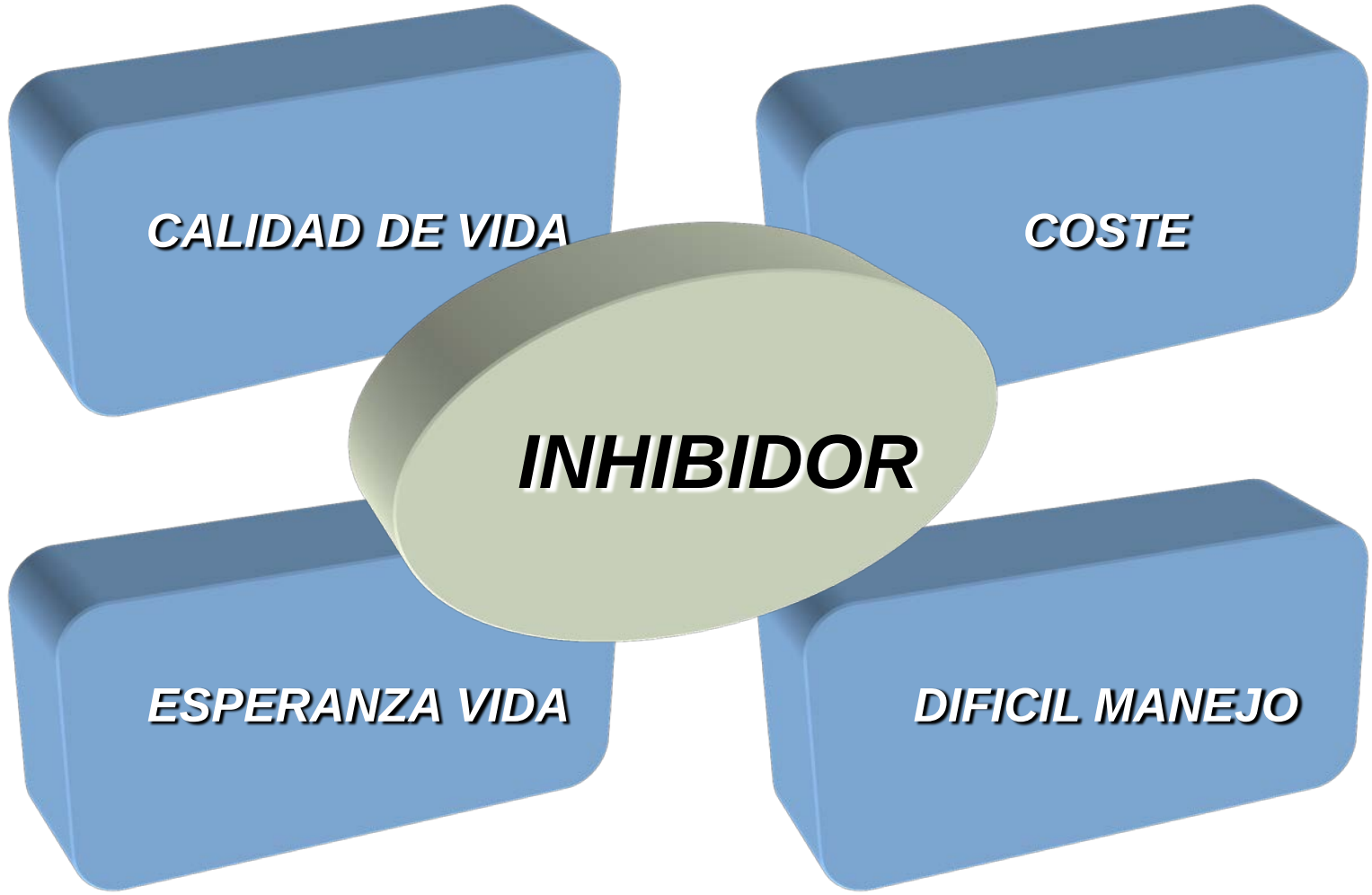
- Incidencia:

  Hemofilia A: 30 %

  Hemofilia B: 1-4 %

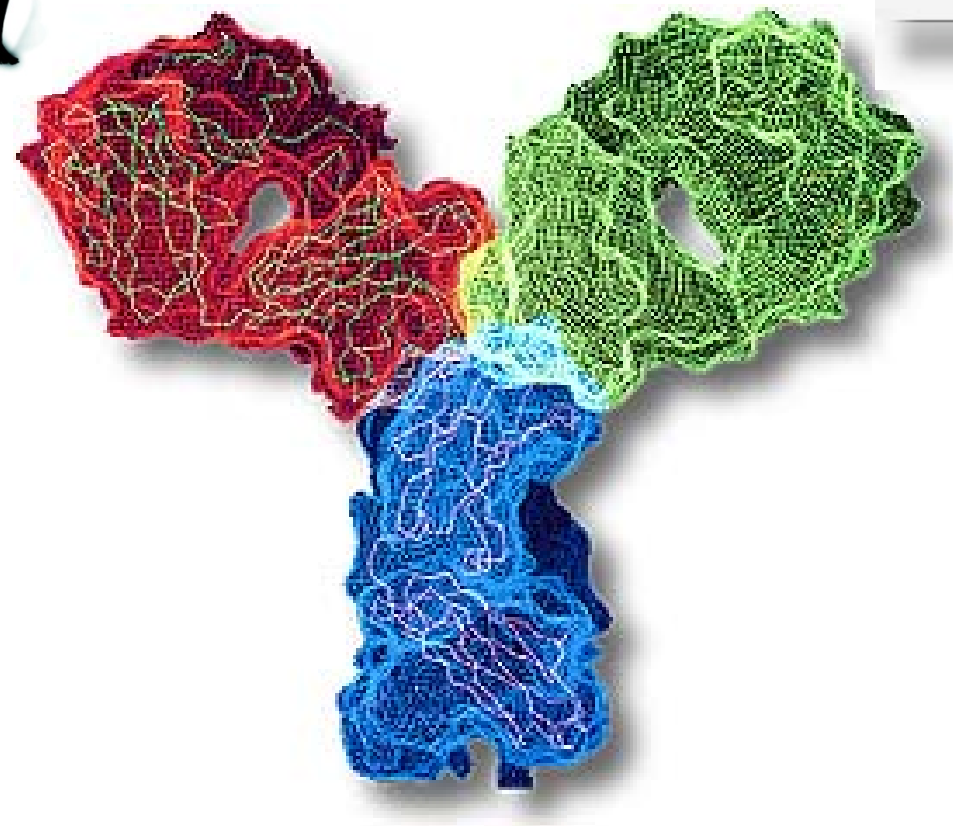
- Prevalencia:

  Hemofilia A: 10-12 %

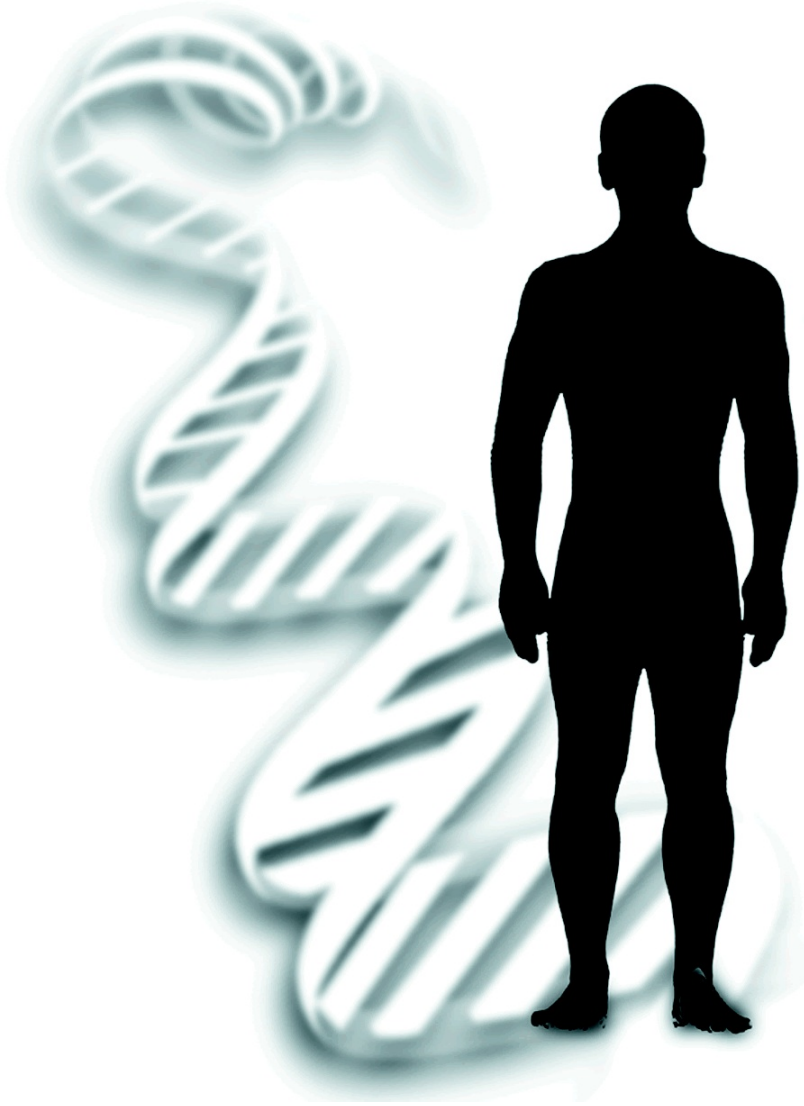

CALIDAD DE VIDA
COSTE
INHIBIDOR
ESPERANZA VIDA
DIFICIL MANEJO

¿POR QUÉ NO TODOS LOS PACIENTES DESARROLLAN INHIBIDOR?

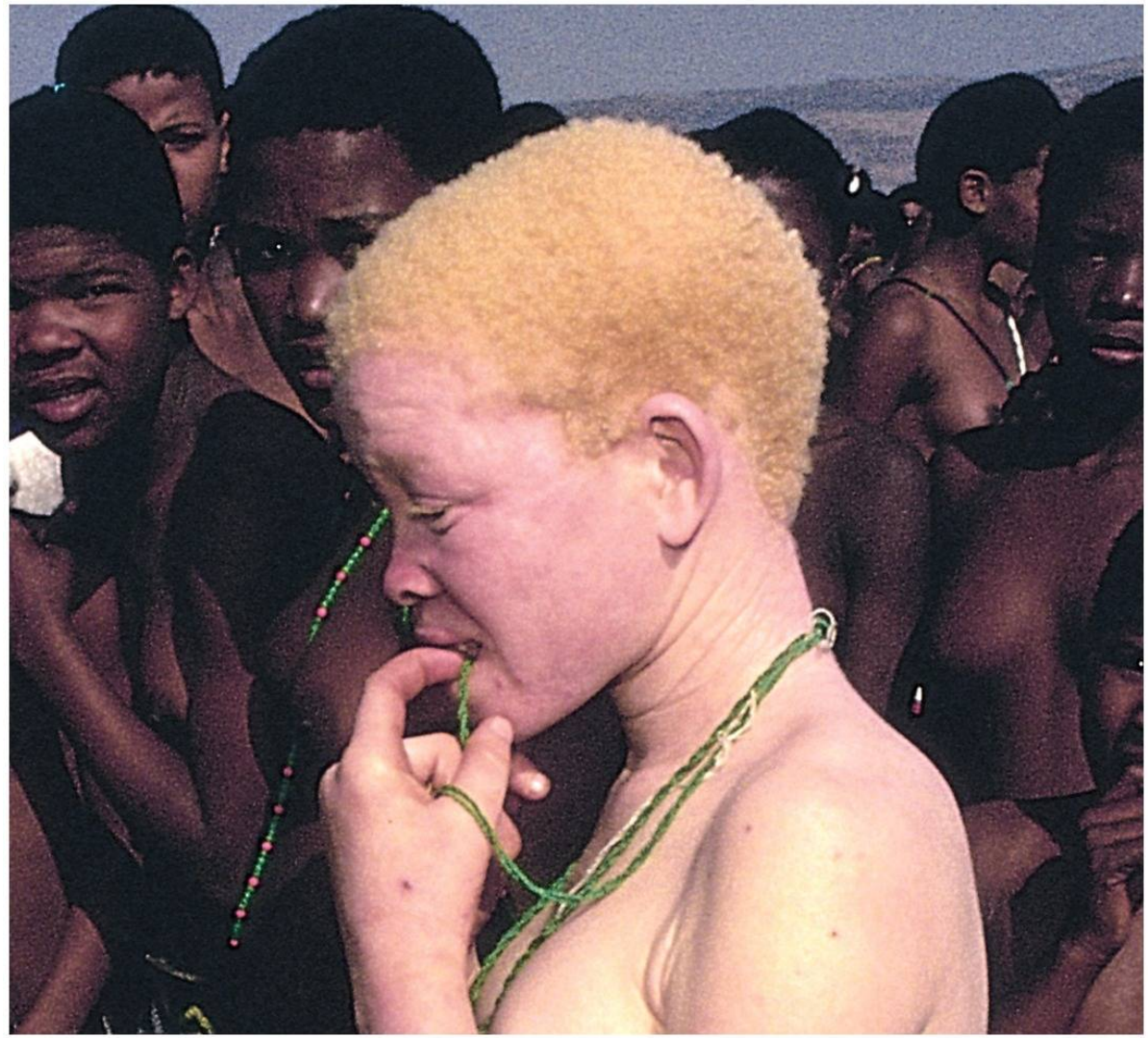
FACTORES IMPLICADOS EN INHIBIDORES



FACTORES GENETICOS

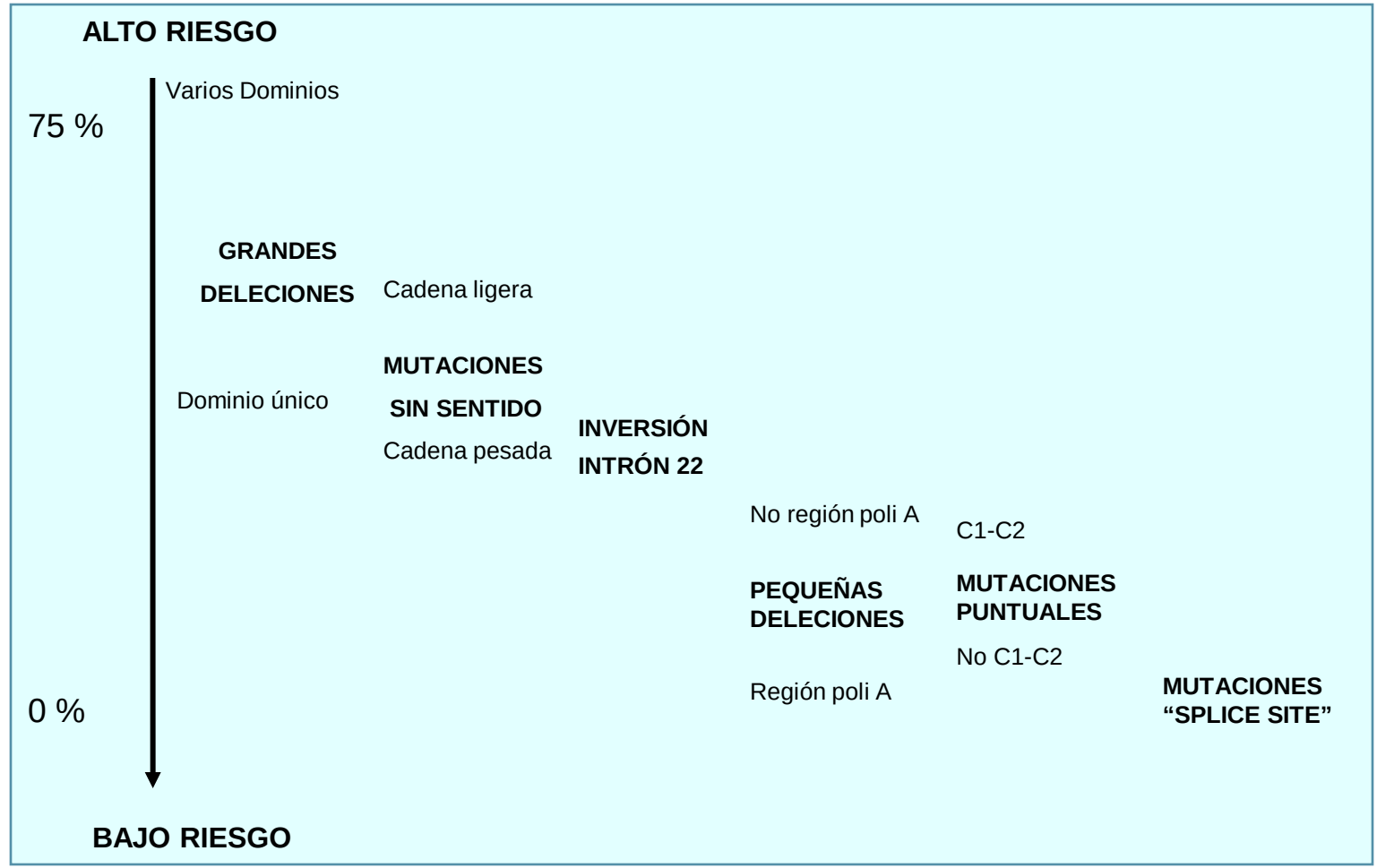


FACTORES GENETICOS



Genotipo y desarrollo de inhibidores

- Factor de riesgo MAS IMPORTANTE:



Genotipo y desarrollo de inhibidores

- ¿Por qué solo un tercio pacientes desarrolla inhibidor?

- FVIII materno: inmunotolerancia
- Sistema inmune diferente
- Inhibición de la respuesta

Genotipo y desarrollo de inhibidores

REVIEW ARTICLE

Cellular immune responses in hemophilia: why do inhibitors develop in some, but not all hemophiliacs?

G. C. WHITE II, C. L. KEMPTON, A. GRIMSLEY, B. NIELSEN and H. R. ROBERTS

Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, Wisconsin, USA and Division of Hematology–Oncology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

To cite this article: White II GC, Kempton CL, Grimsley A, Nielsen B, Roberts HR. Cellular immune responses in hemophilia: why do inhibitors develop in some, but not all hemophiliacs? *J Thromb Haemost* 2005; **3**: 1676–81.

Inmunobiología de los inhibidores

- Respuesta dependiente de linfocitos T

- Desaparición de inhibidores en infección VIH: disminución LT CD4+

  Bray GL et al. Am J Haematol 1993; 42:375-9.

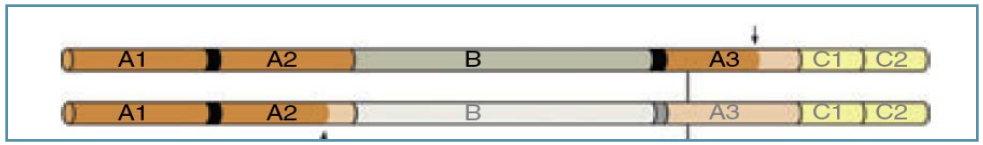
- Aumento IL2 en pacientes con Hemofilia tras FVIII

  Madhok R et al. Br J Haematol 1991; 79:235-8.

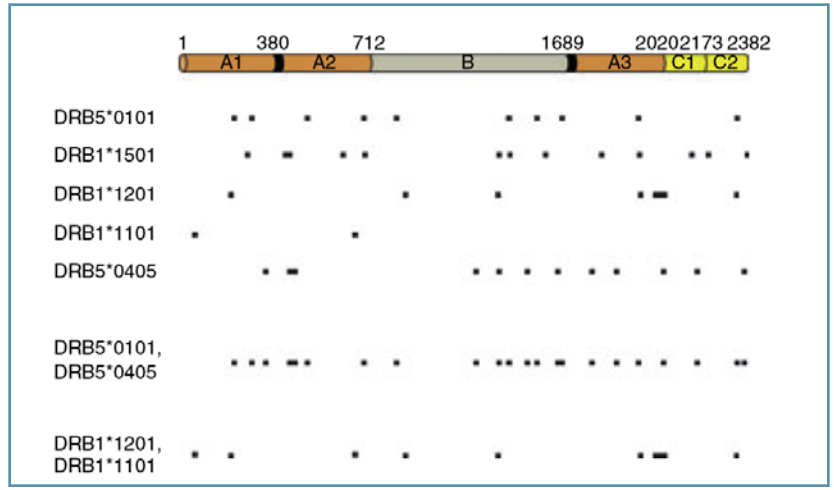
Génetica de HLA y riesgo de inhibidor

- **Polimorfismo de los genes del sistema HLA es un factor de riesgo para el desarrollo de inhibidores (polimorfismo de la IL 10)**

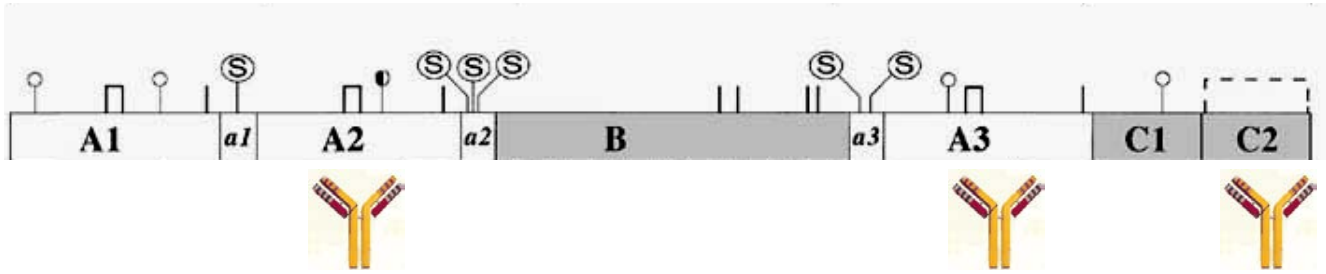
MODELO DE FORMACION DE INHIBIDOR



ALTERACION GENETICA

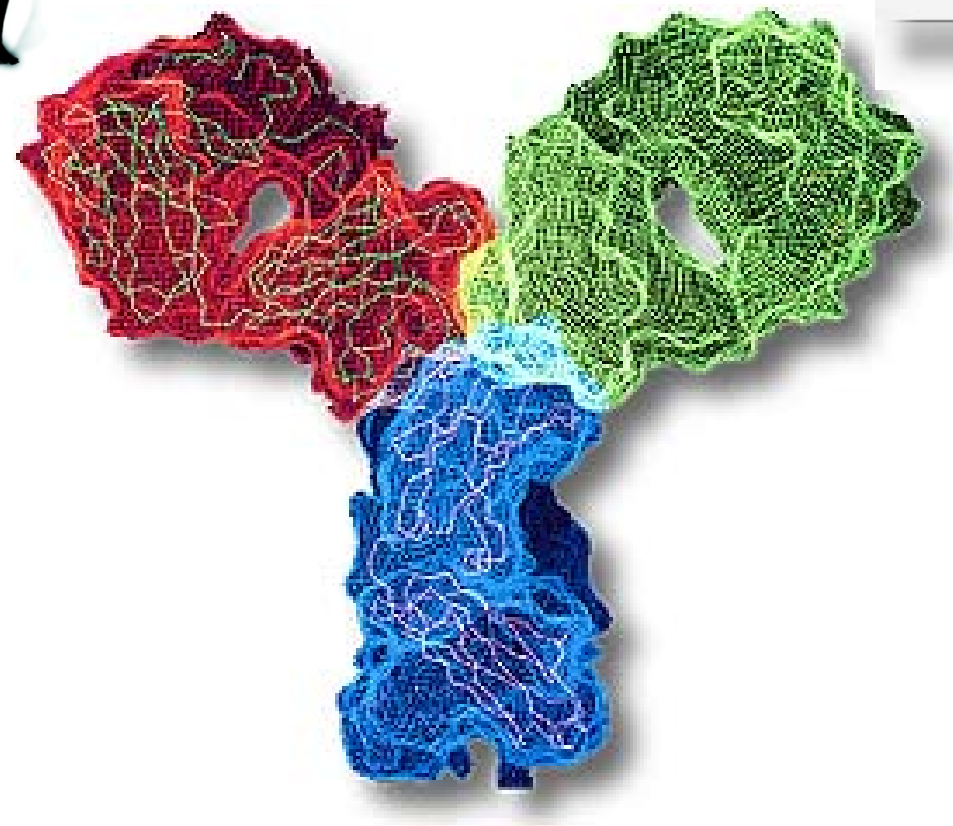


SISTEMA INMUNE



DESARROLLO INHIBIDOR

FACTORES IMPLICADOS EN INHIBIDORES



FACTORES IMPLICADOS EN INHIBIDORES

Riesgo de desarrollo inhibidor

- Tratamiento precoz se asocia a mayor riesgo

- Experiencia española: 62 PPNT

  41% antes 6 meses, 29% 6-12 m, y 12% después 1 año

  Lorenzo JI et al. Br J Haematol 2001; 113: 600–3.

- Experiencia holandesa: 81 PPNT

  31% antes 6 meses, 17% 6-12m,11% 12-18 m y 0% después 18 m.

  Van der Bom JG et al.Haemophilia 2002; 8: 546 (abstract 12 PO 69).

- Estudio Canal:

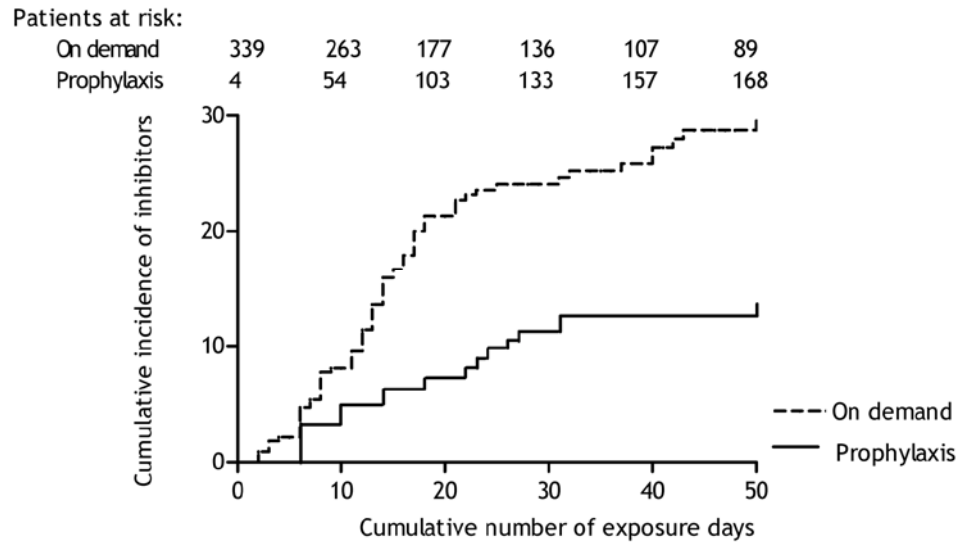
  41% antes 1 m, 30% 1-6 m, 23% en 6-12, 20% entre 12-18 m y 18% después de 18m.

Riesgo de desarrollo inhibidor

•Estudio Canal: Blood, Feb 2007, Publish ahead of print

RELACION CON LA INTENSIDAD MAS QUE CON LA EDAD

MENOR DESARROLLO DE INHIBIDOR EN PROFILAXIS



Profilaxis y riesgo de desarrollo inhibidor

- 50 pacientes

- Inhibidor:
  - Alteración genética
  - Factor
  - Modalidad tratamiento

Haemophilia (2005), **11**, 79–83 DOI: 10.1111/j.1365-2516.2005.00921.x

Prophylactic treatment effects on inhibitor risk: experience in one centre

M. MORADO, A. VILLAR, V. JIMÉNEZ YUSTE, M. QUINTANA and F. HERNANDEZ NAVARRO
Congenital Coagulopathy Section, Haematology Service, Universitary Hospital 'La Paz', Madrid, Spain

Summary. Nowadays, the elective treatment for children with haemophilia is prophylaxis. There is a common consensus that this modality of therapeutic approach is not associated with a higher risk of inhibitor development. We analysed the inhibitor incidence in 50 haemophiliac children and its relationship with mutations, type of clotting factor used and treatment modality. There was a significant correlation between receiving on-demand treatment and an increased incidence of inhibitors, independently of mutations or factor used. We advise putting haemophiliac children under prophylactic treatment as soon as possible, especially if they have mutations associated with high risk of inhibitor development, as prophylaxis is negatively associated with the development of inhibitors.

Keywords: demand, haemophilia, inhibitor, prophylaxis, risk, treatment

Profilaxis y riesgo de desarrollo inhibidor

Inhibidor y modalidad de tratamiento

15 de 19 a la demanda

0 de 31 en profilaxis $p<0.01$

Tipo de mutación y modalidad de tratamiento

Demanda: 17 de 31 mutaciones de alto riesgo

17 de 19 pacientes

Profilaxis: 14 de 31 mutaciones de alto riesgo

14 de 31 pacientes

Profilaxis y riesgo de desarrollo inhibidor

Efecto protector profilaxis

bjh research paper

Environmental risk factors for inhibitor development in children with haemophilia A: a case–control study

Elena Santagostino,[1] Maria Elisa Mancuso,[1] Angiola Rocino,[2] Giacomo Mancuso,[3] Maria Gabriella Mazzucconi,[4] Annarita Tagliaferri,[5] Maria Messina[6] and Pier Mannuccio Mannucci[1]

[1]Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Department of Internal Medicine and Dermatology, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation and University of Milan, Milan, Italy, [2]Haemophilia and Thrombosis Centre, San Giovanni Bosco Hospital, Naples, Italy, [3]Haemophilia Centre, Haematology Department, Haemostasis and Thrombosis Centre, Haematology Unit, 'G. Di Cristina' Children Hospital and University, Palermo, Italy, [4]Policlinico Umberto I Hospital and La Sapienza University, Rome, Italy, [5]Haemophilia Centre, Internal Medicine Unit, Parma Hospital, Parma, Italy, and [6]Centre for Inherited Bleeding and Thrombotic Disorders, Transfusional Unit, "Regina Margherita" Children Hospital, Turin, Italy

Received 23 March 2005; accepted for publication 16 May 2005

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E-mail: hemophilia_ctr@policlinico.mi.it

Summary

This case–control study investigated the interactions between genetic and environmental factors and inhibitor development in 108 children with haemophilia A exclusively treated with recombinant factor VIII (FVIII). Sixty patients with inhibitors were compared with 48 inhibitor-free controls. Family history of inhibitors and null mutations in the *FVIII* gene were more prevalent in cases than in controls (20% vs. 2%, $P = 0{\cdot}001$ and 83% vs. 64%, $P = 0{\cdot}04$, respectively). On the other hand, there was no difference between cases and controls for such putative risk factors of inhibitor development as amniocentesis/villocentesis, premature/caesarean birth, breast-feeding, treatment during infections/vaccinations, surgical procedures and central nervous system bleeding. A trend was found for an increased risk of inhibitor development in children first treated at a young age (<11 months); however, this was not confirmed after adjusting for genetic factors. The implementation of prophylaxis was evaluated as a putative risk factor in a subgroup of 25 cases: seven who started prophylaxis prior to inhibitor development and 18 potentially eligible for prophylaxis because they were inhibitor-free up to the age of 35 months (i.e. the upper limit of the age range at prophylaxis onset in cases and the median age at prophylaxis onset in controls). Patients who started prophylaxis had a lower inhibitor risk than those treated on demand (adjusted odds ratio 0·2, 95% confidence interval 0·06–0·9). The protective effect on inhibitor development shown by prophylaxis may represent an additional advantage prompting its use in haemophilic children.

Keywords: haemophilia, inhibitors, risk factors, prophylaxis, FVIII gene mutations.

Inflamación y riesgo de desarrollo inhibidor

- Inflamación en coexistencia con FVIII: riesgo de inhibidor.

- Terapia génica
  - En perros y monos inmunotolerantes a FIX canino y humano desarrollaron inhibidor cuando se sintetizo FIX por terapia génica con vectores virales a nivel hepático.

  - Modelos caninos de hemofilia terapia génica a nivel muscular la infección de la piel aumenta el riesgo de inhibidor.

    Kaufman RJ. Hum Gen Ther 1999; 19:2091-2107.

- Experiencias individuales
  - Vacunas, infecciones, cirugía en el momento de las primeras exposiciones

Tipo de producto y riesgo de desarrollo inhibidor

Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A

Jenny Goudemand, Chantal Rothschild, Virginie Demiguel, Christine Vinciguerrat, Thierry Lambert, Hervé Chambost, Annie Borel-Derlon, Ségolène Claeyssens, Yves Laurian, Thierry Calvez, and the members of the FVIII-LFB and Recombinant FVIII study groups

Inhibitor development is the major treatment complication in children with severe hemophilia A. It is not clear whether the risk of inhibitors is higher with recombinant factor VIII or with plasma-derived factor VIII. We used multivariate analysis to compare 2 cohorts of previously untreated patients (PUPs) with severe hemophilia A: 62 patients treated with the same brand of high-purity plasma-derived FVIII (pFVIII) containing von Willebrand factor (VWF) and 86 patients treated with full-length recombinant FVIII (rFVIII). In addition to the usual end points (all inhibitors, high inhibitors), we also examined a third end point (high inhibitors and/or immune tolerance induction). The risk of inhibitor development was higher in patients treated with rFVIII than in patients treated with pFVIII, regardless of other risk factors (*F8* genotype; nonwhite origin; history of inhibitors in patients with a family history of hemophilia; age at first FVIII infusion). The adjusted relative risk (RRa) for inhibitor development with rFVIII versus pFVIII was 2.4 (all inhibitors), 2.6 (high inhibitors), and 3.2 (high inhibitors and/or immune tolerance induction), respectively, depending on the end point (above). The pathophysiology of this large effect must be understood in order to improve the characteristics of recombinant products and to reduce the incidence of inhibitors to FVIII. (Blood. 2006;107:46-51)

Introduction

Tipo de producto y riesgo de desarrollo inhibidor

- Estudio Canal: Blood próxima publicación

- Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study

- "In conclusion, our findings do not support the notion that plasma-derived factor VIII products with considerable concentrations of von Willebrand factor confer a lower risk to develop inhibitory antibodies than recombinant factor VIII products. Additionally, switching between factor VIII product brands did not increase inhibitor risks in these previously untreated patients with severe haemophilia A"

DETECCION DE INHIBIDORES

- DETECCION CLINICA
  - Altos requerimientos de factor para frenar hemorragias
  - Ausencia de respuesta a la dosis calculada

- DETECCION LABORATORIO
  - Estudios de Mezclas
  - Estudios de recuperación
  - Cuantificación inhibidor
  - Vida media

CLASIFICACION DE INHIBIDORES

- Bajo título de inhibidor o bajo respondedor:

  <5 Unidades Bethesda (U.B. ó B.U.)

  No respuesta anamnésica

- Alto título de inhibidor o alto respondedor

  >5 Unidades Bethesda

  Respuesta anamnésica

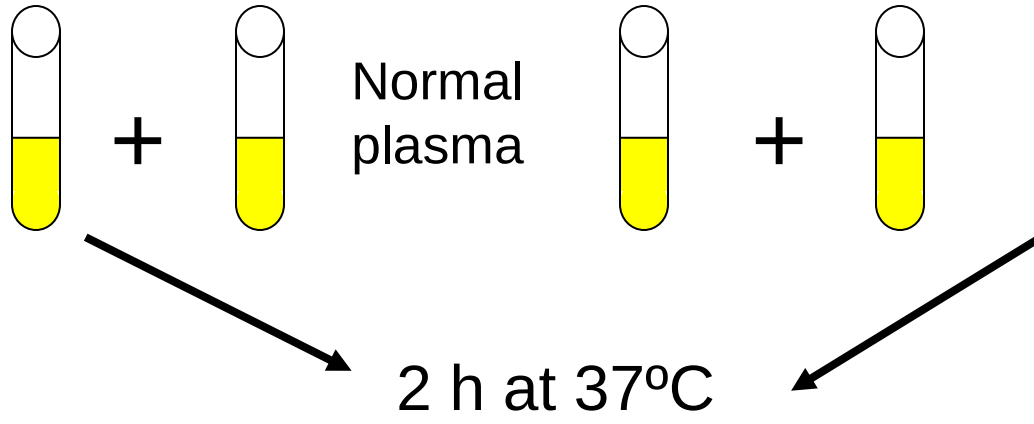
CUANTIFICACION DE INHIBIDORES

METODO BETHESDA. 1975 (Kasper)

PACIENTE

CONTROL

Plasma del paciente



1 UB destruye el 50% actividad FVIII en plasma normal

¿COMO TRATAR LOS PACIENTES CON HEMOFILIA E INHIBIDOR?

CON MUCHA DIFICULTAD

EXPERIENCIA

CONOCIMIENTO

TRATAMIENTO INHIBIDORES

- CORTO PLAZO: control episodios hemorrágicos

- LARGO PLAZO: erradicación inhibidores

ESTRATEGIAS TERAPEUTICAS EN INHIBIDOR

Haemophilia (2005), **11**, 611–619 DOI: 10.1111/j.1365-2516.2005.01161.x

GUIDELINES

Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors

A. GRINGERI and P. M. MANNUCCI, FOR THE ITALIAN ASSOCIATION OF HAEMOPHILIA CENTRES

Department of Internal Medicine and Dermatology, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Policlinico, Mangiagalli and Regina Elena Hospital Foundation and University of Milan, Milan, Italy

ESTRATEGIAS TERAPEUTICAS

- Tratamiento sustitutivo

Factor VIII/FIX humano
Factor VIII Porcino

- Agentes “Bypassing”

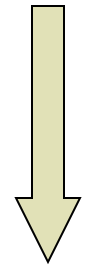
CCPA (FEIBA®)
rFVIIa (NovoSeven®)

- Erradicación de Inhibidores

Inmunoadsorción
Inducción de Tolerancia Inmune (ITI)
Immunosupresión

TERAPIA ENCAMINADA A ERRADICAR EL INHIBIDOR

OBJETIVO TRATAMIENTO
EN LOS PACIENTES CON INHIBIDOR



TOLERANCIA INMUNE

CONCEPTO DE INMUNOTOLERANCIA

- Eliminación del inhibidor
- Normalización de la vida media del factor administrado
- Ausencia de respuesta anamnésica

INMUNOTOLERANCIA:ALTAS DOSIS DE FACTOR

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.

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

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

1. Allain, J. P., Prommel, D. *Blood*, 1976, **47**, 937.
2. Dormandy, K., Hawkey, C., Churchill, W. G. J., Cowley, J. *Thromb. Diath. haemorrh.* 1971, **43**, 355.
3. Nielsson, I. M., Hedner, U. *Scand. J. Haemat.* 1976, **16**, 364.
4. Mannucci, P. M., Bader, R., Ruggeri, Z. M. *Lancet*, 1976, i, 41.
5. Brackmann, H. H., Bazel, F., Hofmann, P., Egli, H. *Thromb. Haemorrh.* 1977, **38**, 369 (abstr).

INMUNOTOLERANCIA:ALTAS DOSIS DE FACTOR

- BRACKMANN (1977): PROTOCOLO DE BONN

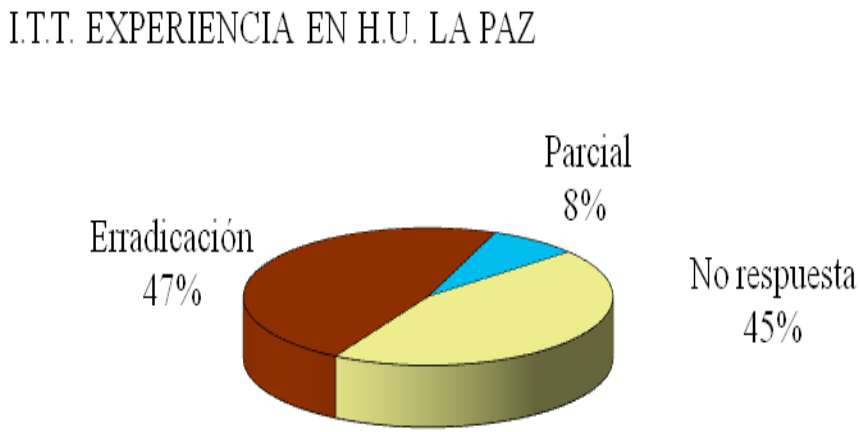
FASE I: 100 U FVIII/12 horas
50 U Feiba®/12 h
Se administrará hasta que el inhibidor sea inferior a 1 U.B.

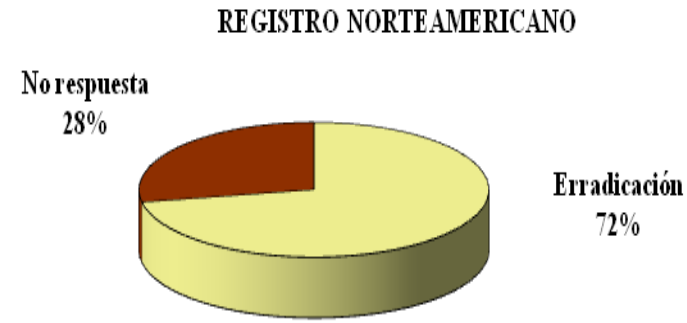
FASE II: 100 U Factor VIII/12 horas
Se administrará hasta que desaparezca el inhibidor

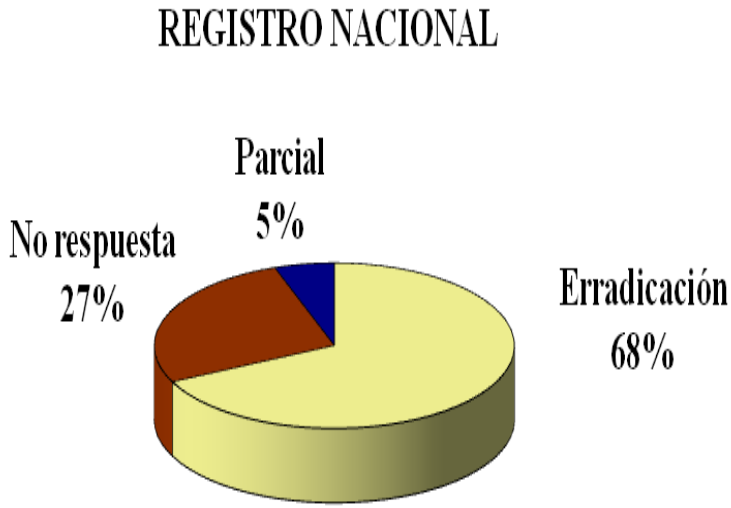
FASE III: 100 U Factor VIII/24
Se administrará hasta la normalización de la vida media del factor

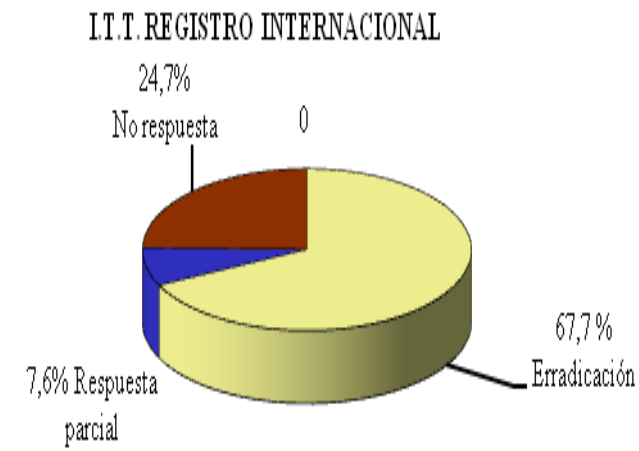
FASE IV:
Suspender el tratamiento. Administrar tratamiento a la demanda o en régimen de profilaxis

EXPERIENCIA ITT

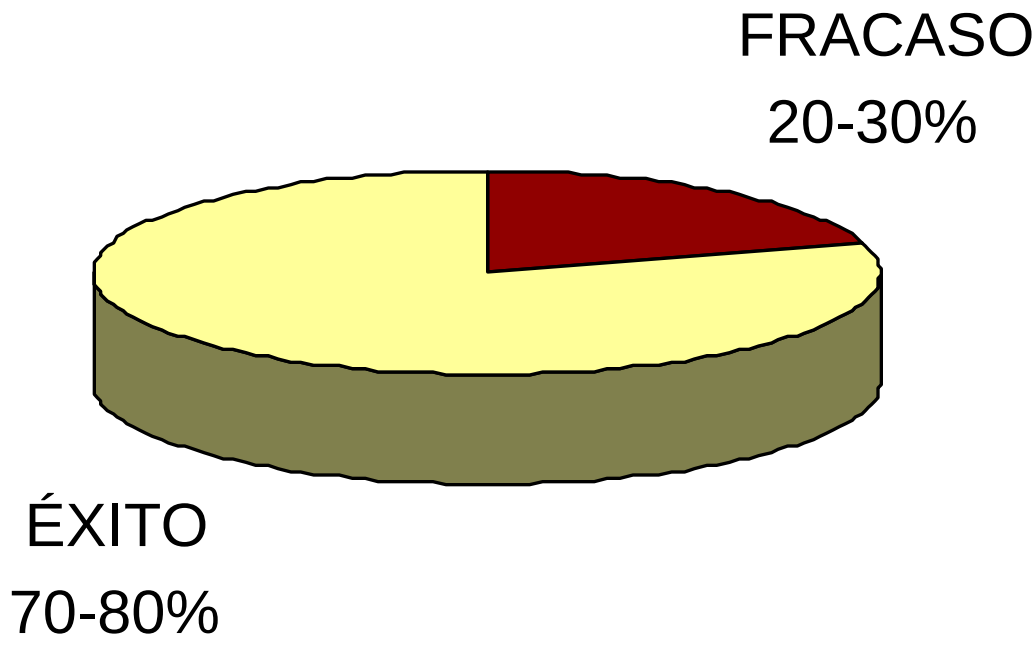








RESPUESTA GLOBAL



TRATAMIENTO DE LOS EPISODIOS HEMORRAGICOS EN PACIENTES HEMOFILICOS CON INHIBIDOR

TRATAMIENTO DE LOS EPISODIOS HEMORRAGICOS

Bajo título de inhibidor (<5 U.B.)

Concentrados factor VIII a altas dosis

Alto título de inhibidor (>5 U.B.)

FVIII porcino (Hyate-C®)

CCPA (Feiba®/Autoplex®)

rFVIIa (Novoseven®)

CONSIDERACIONES FINALES

- El desarrollo de anticuerpos: la complicación más importante del tratamiento de los pacientes con hemofilia.

- Incidencia acumulada: 25-32%.
- Prevalencia: 12%. Carácter transitorio
  - *Key NS. Br J Haematol 2004; 127:379-391.*

- Tratamiento sustitutivo inefectivo

CONSIDERACIONES FINALES

- Tratamiento muy complejo

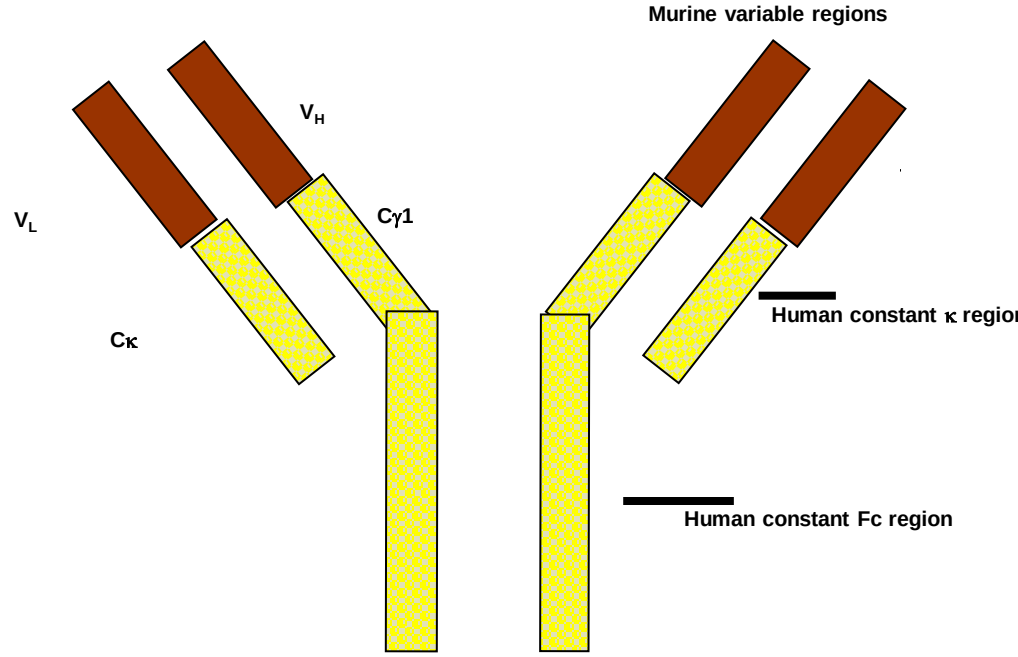
- Farmacos con eficacia en torno 80%

- FVIIar (NovoSeven®): 90-120 µgr/kg CADA 2 horas
  Bolos más elevados: 270µgr/kg

- CCPA (FEIBA®): 50-100 unid/8-12 h
  (nunca sobrepasar 200 unid/kg día)

Anti-CD20

- Inmunoglobulina Ig G1 quimérica (humana-murina) que produce citotoxicidad de los linfocitos B CD20+
- Utilizado de forma extendida en neoplasias linfoides B
- Procesos autoinmunes: LES, AHAI, Aplasia pura celulas rojas, PTI.



Inmunotolerancia y Anti-CD20

LIMITACIONES:

- Utilización limitada en niños
- Mayor efecto en autoinmunidad
- No tiene efecto sobre célula plasmática
- Comienzo efecto variable (desde 4 días hasta 2-3 meses)
- Inmunosupresión de 6-9 meses duración.

Inmunotolerancia y Anti-CD20

bjh short report

Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia

Mary Mathias, Kate Khair, Ian Hann and Ri Liesner

Haemophilia Centre, Great Ormond Street Children's Hospital, London, UK

 British Journal of Haematology, **125**, 366–368

Inmunotolerancia y Anti-CD20

¿Utilización de Ac anti-CD20 (Mabthera) en Hemofilia Congénita con inhibidor y fracaso a ITI?

Inmunotolerancia y Anti-CD20

- CONCLUSIONES:
- Respuesta en pacientes con fracaso a ITI
- Independiente del tiempo de instauración inhibidor
- Importante la disminución de niveles de linf B
- Títulos bajos de inhibidor
- ASOCIACION SIMULTANEA DE FACTOR

Inmunotolerancia y Tacrolimus

- TACROLIMUS:

- Inmunosupresor utilizado en la prevención del rechazo en aloinjerto renal y hepático

- Tratamiento del rechazo en aloinjerto renal, cardiaco y hepático

- No existe experiencia en Hemofilia

Inmunotolerancia

- Aporta una inmunosupresión añadida a anti-CD20
- Actualmente desaparición del inhibidor con vida media normal
- Cuando retirada de inmunosupresión
- ¿Futuro?. En general una vez lograda ITT no se pierde.

Inmunotolerancia
Utilización de Concentrados de FVIII/FvW (®Fanhdi)

EXPERIENCIA EN EL HOSPITAL UNIVERSITARIO LA PAZ. MADRID

Inmunotolerancia
Utilización de Concentrados de FVIII/FvW (®Fanhdi)

- Escasa formación de inhibidores
- Menos reactivos con los antiFVIII
- Prolongación de la exposición antigénica del FVIII al sistema inmune
- Ocultan los epítopes del FVIII
- Preservan la conformación del FVIII, lo que incrementa la inducción a la tolerancia
- Altas dosis pueden suprimir la memoria de las células B

Inmunotolerancia
Experiencia en el HULP

Número de pacientes	8
Niños	6
Adultos	2
Pico máximo del inhibidor pre-Inmunotolerancia	8-256 U.B.
Concentrado administrado previo a la aparición del inhibidor	
Recombinante:	5 casos
Plasmáticos desprovistos de factor	3 casos

Inmunotolerancia
Experiencia en el HULP

TIPO DE INMUNOTOLERANCIA

Primaria:	**5 casos**
Rescate:	**3 casos**

Inmunotolerancia
Experiencia en el HULP
Utilización de Concentrados de *FVIII/FvW (®Fanhdi)

DOSIS UTILIZADA

200 U.I./Kg/diarios	5 casos
100 U.I./Kg/diarios	3 casos

* ®Fanhdi: Relación FVIII/FVIIIRCO -> 1/1,5

Inmunotolerancia

Utilización de Concentrados de *FVIII/FvW (®Fanhdi)

Experiencia en el HULP

RESULTADOS

*Buena respuesta	7 (14 meses)
Fracaso	1 (14 meses)

*Buena respuesta: desaparición del inhibidor y v.m. normal
Los pacientes continúan en la actualidad en profilaxis

Inmunotolerancia
Utilización de Concentrados de *FVIII/FvW (®Fanhdi)
Experiencia en el HULP

CONCLUSIONES

Se confirman las observaciones de otros estudios de la importancia de los concentrados plasmáticos ricos en factor v Willebrand para obtener buena respuesta

CASO:

- Niño de 3 años

- Antecedentes familiares: Abuelo con Hemofilia A grave fallecido

- FVIII:C: 0%. Alteración molecular: inversión del intrón 22

- Nacimiento: vía vaginal. Venopunción de vena femoral.
  Pseudoaneurisma de arteria femoral.

- A los tres meses de vida:
  embolización de aneurisma bajo cobertura de FVIII recombinante
  Episodio de isquemia transitoria: heparina IV

CASO:

- Tras 21 exposiciones a FVIII: DESARROLLO DE INHIBIDOR

- Título: 1.96 UB

CASO:

- 1ª INMUNOTOLERANCIA: 200 unid/kg/24 con el producto que desarrolló inhibidor (recombinante).

- FRACASO: 24 UB

- 2ª INMUNOTOLERANCIA: 200 unid/kg/24 h con FVIII rico en FvW (®Fanhdi).

- FRACASO: 78 UB

- 3ª INMUNOTOLERANCIA: 200 unid/kg/24 con FVIII rico en FvW (®Fanhdi) asociado a Anti-CD20 y Tacrolimus

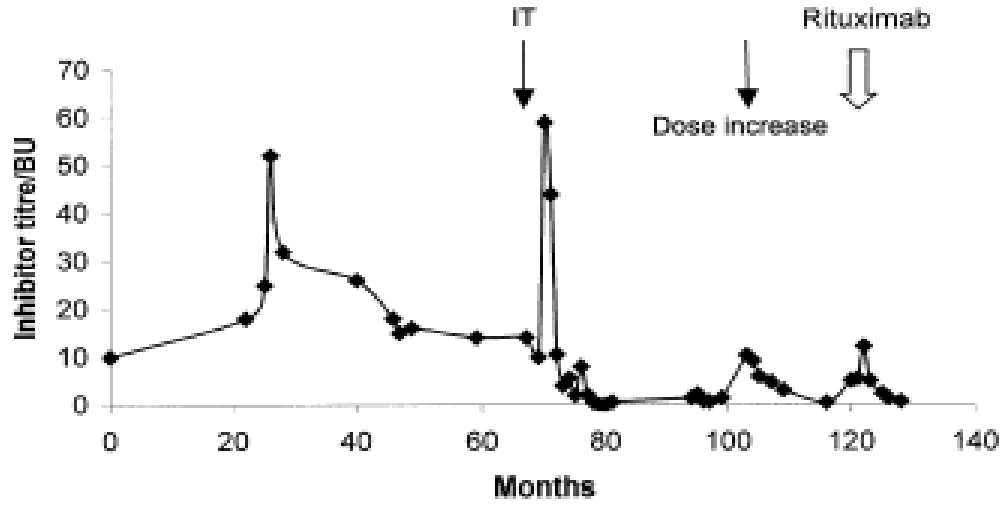
CASO:

- Al mes del inicio: 2.2 UB
- A los dos meses 0 UB
- A los 6 meses normalización en la vida media

- ÉXITO EN LA INMUNOTOLERANCIA

Inmunotolerancia y Anti-CD20

- <u>CASO :</u>
- Hemofilia A grave. 11 años. Fracaso ITI.
- Titulo inhibidor 12 UB antes Rituximab + FVIII/48 h
- Indetectable 11 meses.
- Disminución de Linf B CD19+



Inserm

Institut national
de la santé et de la recherche médicale

UNIVERSITE PIERRE & MARIE CURIE
LA SCIENCE A PARIS

Immunological role of VWF in preventing inhibitors…

Sébastien Lacroix-Desmazes

INSERM U872 Equipe 16
Immunopathologie et immunointervention thérapeutique, Paris, France

ISTH 2007

Protective effect of VWF on FVIII immunogenicity

PUPS studies

Goudemand, Blood, 2006

Recombinant FVIII	30.0%
Plasma-derived FVIII	11.0%

Gouw, Blood, 2007

No difference between pdFVIII and rFVIII

ObsITI -
Investigating the role of VWF in ITI

Wolfhart Kreuz, C. Escuriola Ettingshausen,
C. Königs and the ObsITI-Study-Team

Johann-Wolfgang-Goethe University Hospital
Dept. Of Pediatrics
Hemophilia Comprehensive Care Centre

Therapy regimens for inhibitor elimination

Bonn Protocol (high-dose protocol)

LR: 50-100 IU FVIII/kg bw daily or every other day

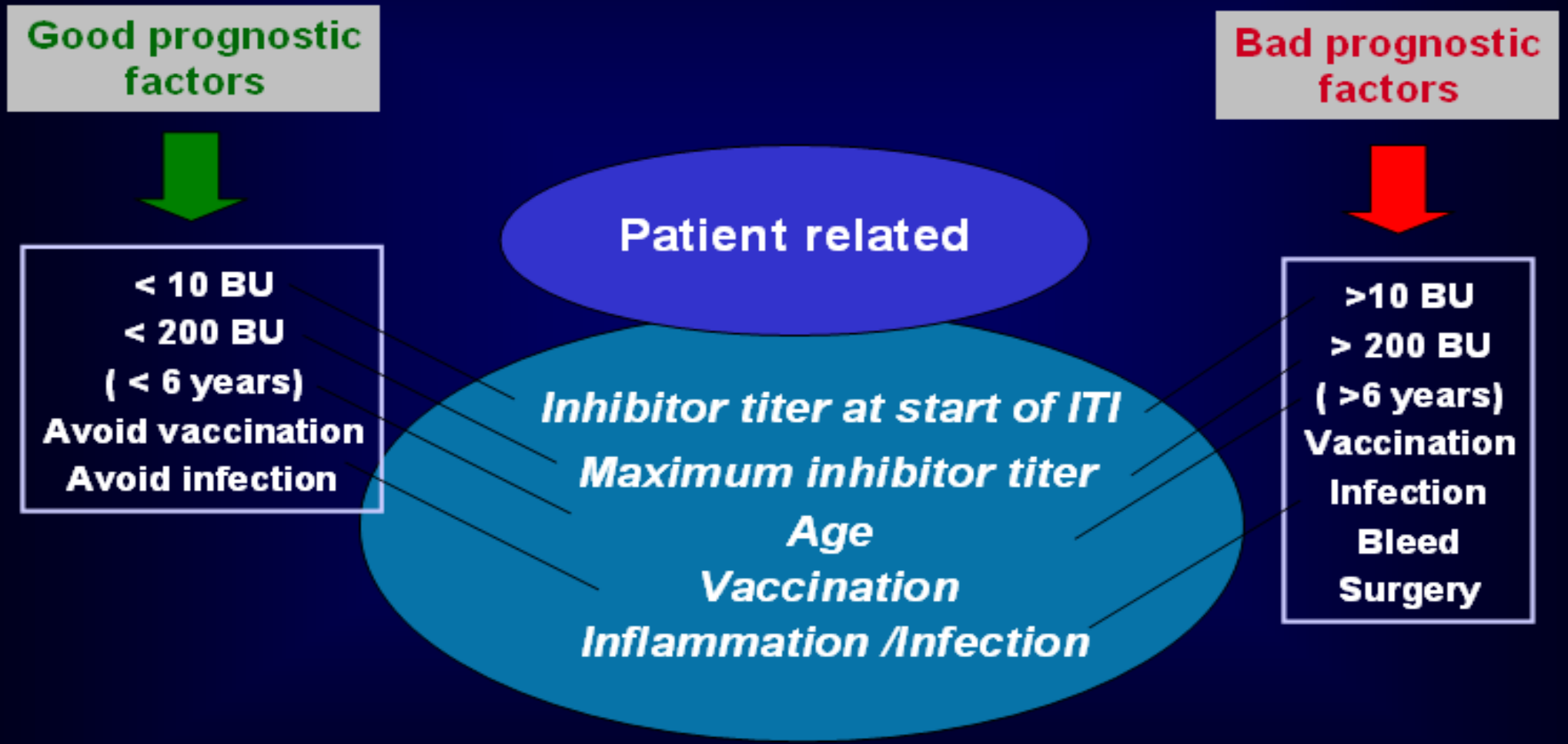
HR: 100-150 IU FVIII/kg bw every 12 hours; according to the bleeding tendency concomitant treatment with FEIBA® (Baxter) 50-100 IU/kg bw once or twice daily

Malmö Protocol

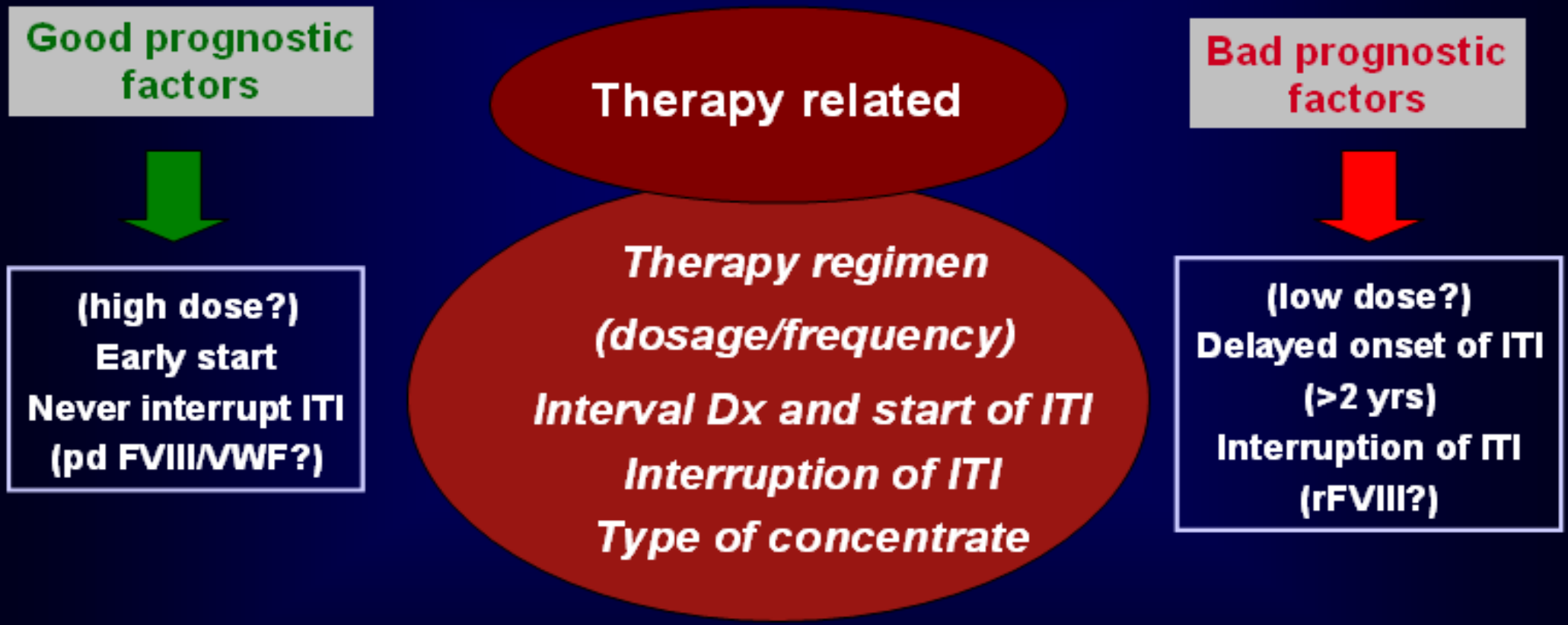
Extracorporal immune adsorption with Protein-A-columns, immunosuppression (cyclophosphamid), IVIG and FVIII administration

Intermediate dose protocols

Variables which may have impact on the success rate of Immune tolerance induction (ITI)



Variables which may have impact on the success rate of Immune tolerance induction (ITI)



Use of FVIII/VWF in inhibitor patients after failure of earlier ITI

Author	No of pts [n]	HR [n]	Therapy regimen	Product	Therapy duration [months]	Outcome
Orsini et al., 2005	8	8	50-230 IU/kg BW	FVIII-VWF complex concentrate	8 (median)	7/8 complete success 1 partial success
Gringeri et al, 2006	4	4	200 IU/kg BW	FVIII-VWF complex concentrate		3/4 complete success

Success rates of Immune tolerance induction therapy - Hemophilia Centers Bonn and Bremen -

	<1990 n=51	≥1990-7/2001 n=42	
	Plasma-derived FVIII	Recombinant FVIII (n=14)	Plasma-derived FVIII (n=28)
Overall success rate	87%	54%	82%
Success rate (high responder >5BU)	86%	43%	78%
Success rate (low responder >0,6-5BU)	93%	72%	91%

[Auerswald G, Spranger Th, Brackmann HH; Haematologica, 2003]

ObsITI -

Observational Immune Tolerance Induction Research Program

ObsITI - Observational Immune Tolerance Induction Research Program

- International open-label, uncontrolled, multi-centre observational program initiated by the Paediatric Haemophilia Center, Frankfurt, Germany (started in 12/2005)
- Co-operating centre: Malmö, Sweden (in-vitro test TGA; E. Berntorp, J. Astermark)
- ITI according to the Bonn protocol
- All types of F VIII concentrates
- Retrospective study arm (approx. 100 patients)
- Prospective study arm (approx. 100 patients)

ObsITI (Observational Immune Tolerance Induction) Research Program

Does variation in in-vitro inhibitory activity against different types of F VIII concentrates (measured by two different in-vitro tests) have any clinical significance?

- Concerning duration and rate of ITI success

ObsITI - Observational Immune Tolerance Induction Research Program

In-vitro-Tests

- In-vitro-test (plasma sample before start of ITI)
- Variation of inhibitor reactivity with different F VIII concentrates: Different types of concentrates are mixed with patient inhibitor plasma. After 2 hrs of incubation at 37°C the F VIII:C activity of the test mixture is measured, compared with a control mixture and calculated by a standard Bethesda log units scale.

  (University Hospital Frankfurt, W. Kreuz and team)

ObsITI - Observational Immune Tolerance Induction Research Program

In-vitro-Tests

- **In-vitro-test 2 (Haemostatic role of variation of inhibitor reactivity with different F VIII concentrates): Different types of concentrates are mixed with patient inhibitor plasma and thrombin generation is measured**
- **(Malmö University Hospital, E. Berntorp, J. Astermark)**

ObsITI - Investigation of the possible influence of the following variables on duration and success of ITI

- Patient age at start of Immune Tolerance Induction
- Inhibitor titres (both at start of ITI and peak titres)
- Vaccination
- Surgical procedures, bleeds
- Inflammatory status during ITI (CVL infections)
- Mutation type
- Number of EDs between inhibitor development and start of ITI
- Dose and frequency of F VIII administration
- Purity of F VIII used
- Epitope mapping and IgG subclass analysis of F VIII inhibitors during ITI
- Impact of in-vitro tests
  (using a modified Oxford method as well as TGA)

ObsITI - Observational Immune Tolerance Induction Research Program

Inclusion criteria

- Male patients
- No age limits
- Haemophilia A patients with clinical relevant inhibitor levels (>0.6 BU)
- ITT for the first time or earlier ITI failure
- ITI according to the Bonn protocol recommended
- Informed consent

ObsITI (6/2007)

Patients

- Number of inhibitor patients (> 0.6 BU) included and data entered until June 2007
- n=47 (22 completed; 23 ongoing; 2 withdrawn*)
- 14 participating centers
  - Russia (Kirov/Chernova, Moscow Izmailovskaya/Vdovin, Moscow/Plyushch, St. Petersburg/Andreeva)
  - Portugal (Porto/Campos and Carvalho, Coimbra/Felipe, Lisbon/Rosado, Freitas, Almida, Diniz, Antunes)
  - Germany (Frankfurt/ Kreuz, Münster/Nowak-Göttl)
  - Austria
  - Slovenia
  - Spain

* n=1 insufficient compliance; n=1 failure

ObsITI - Observational Immune Tolerance Induction Research Program

Preliminary results- Recruited patients

Country	Number of recruited patients	Documentation completed
Austria	1	0
Germany	28	19
Portugal	16	5
Russia	23	1
Slovenia	1	0
Spain	2	0
Total	71	24

Interim analysis 6/2007

ObsITI

Therapy regimen

- **Bonn Protocol (recommended)**

  LR: 50-100 IU FVIII/kg bw daily or every other day

  HR: 100-150 IU FVIII/kg bw every 12 hours; according to the bleeding tendency concomitant treatment with FEIBA® (Baxter) 50-100 IU/kg bw once or twice daily

  Dosage tapered when inhibitor is negative, F VIII recovery and half-life normal

ObsITI

ITI treatment results for completed / withdrawn patients

ITI result	N	%
COMPLETE SUCCESS	21	87.5
PARTIAL SUCCESS	1	4.17
TREATMENT FAILURE	2	8.33
Total	*24*	*100*

Success of ITI

- **Complete Success (Inhibitor titre <0.6 at least at two consecutive times; normal FVIII recovery and half-life)**
- **Partial Success (2 of 3 criteria above met)**
- **Partial response (1 of 3 criteria above met)**
- **Failure (none of the criteria above met)**

Inmunotolerancia de rescate

Experiencia en el HULP

PROTOCOLO*

Día 0: Evaluación inicial

Día 1: Premedicación (Actocortina 100 mg iv + Nolotil 1 amp iv + Polaramine 2 mg iv) + RITUXIMAB: 375 mg/kg/iv en 4 horas

Este ciclo se repetirá los días 8, 15 y 22

Desde el día 1 hasta el día 22 se administrará por vo Metilprednisolona a la dosis de 1 mg/Kg/día

A partir de día 23 se administrará concentrado de FVIII rico en FvWillebrand a la dosis de 200 U.I./Kg/día

***cuando el inhibidor presente título > 10 U.B. se someterán a columnas de absorción**

Inmunotolerancia de rescate
Experiencia en el HULP

TRATAMIENTO PROFILÁCTICO DE LAS INFECCIONES

INMUNOGLOBULINAS 0,4 GR/KG/IV CADA 21 DÍAS

TRIMETROPIN SULFAMETOXAZOL (®SEPTRIM) 1 comp/12 h/48 h

Inmunotolerancia de rescate
Experiencia en el HULP
REEVALUACIÓN A LOS 30 DÍAS

Se mantendrá el tratamiento con Concentrados de FVIII ricos en FvWillebrand a la misma dosis.

Se seguirá con la profilaxis infecciosa (®Septrim e Inmunoglobulinas)

Inmunotolerancia de rescate

Experiencia en el HULP

REEVALUACIÓN A LOS 60 DÍAS

Si se produce RESPUESTA COMPLETA (inhibidor negativo y vida media normal) se mantendrá el tratamiento con Concentrados de FVIII ricos en FvWillebrand a la misma dosis y la profilaxis infecciosa (®Septrim e Inmunoglobulinas)

Inmunotolerancia de rescate
Experiencia en el HULP
REEVALUACIÓN A LOS 60 DÍAS

Si se produce FALTA DE RESPUESTA se iniciará un TRATAMIENTO INMUNOSUPRESOR ADICIONAL (Tracolimus o micofenolato)

La dosis de TRACOLIMUS será de 0,3 ml/kg/día, que se mantendrá durante un año. Simultáneamente se administrará METILPREDNISOLONA a la dosis de 1 mg/kg/día. Seguirá manteniéndose la profilaxis infecciosa con Inmunoglobulinas y ®Septrim

Inmunotolerancia de rescate
Experiencia en el HULP
REEVALUACIÓN A LOS 90 DÍAS

Si la RESPUESTA COMPLETA se mantiene, mantener el tratamiento profiláctico con concentrados de FVIII/FvW

Cuando se administre TRACOLIMUS o MICOFENOLAT se mantendrán durante 1 año.

Una vez conseguida la RESPUESTA COMPLETA se harán reevaluaciones cada 3 meses

Inmunotolerancia de rescate
Utilización de Concentrados de *FVIII/FvW (®Fanhdi)
Conclusiones

- ✓ **Prolongan la presentación antigénica del FVIII al sistema inmune**
- ✓ **Los inhibidores del FVIII con especificidad para el dominio C2 presentan menor actividad inhibitoria frente al FVIII/FvW**
- ✓ **El FvW del concentrado FVIII/FvW oculta los epítopes del FVIII**