VII
Jornadas Farmacéuticas
sobre el tratamiento de las
COAGULOPATÍAS
CONGÉNITAS
MADRID 12,13 Y 14 de Diciembre de 2012

HOSPITALES UNIVERSITARIOS
VIRGEN DEL ROCÍO

IMPACTO DEL TRATAMIENTO DE LAS COAGULOPATÍAS CONGÉNITAS EN EL SERVICIO DE FARMACIA

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La hemofilia en números:

- En el mundo: 400.000 personas padecen Hemofilia A o B

- En España: cerca de 3.000

- La incidencia de la Hemofilia A es de 1 de cada 5.000 varones nacidos (87%); en el caso de la Hemofilia B es de 1 de cada 30.000 (13%).

45% de las personas con hemofilia son graves (< 1% de factor de coagulación)

10% moderados (entre el 1 y el 5% de factor)

45% restante son leves (entre el 6 y el 30%).

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The national registry of haemophilia A and B in Spain: results from a census of patients

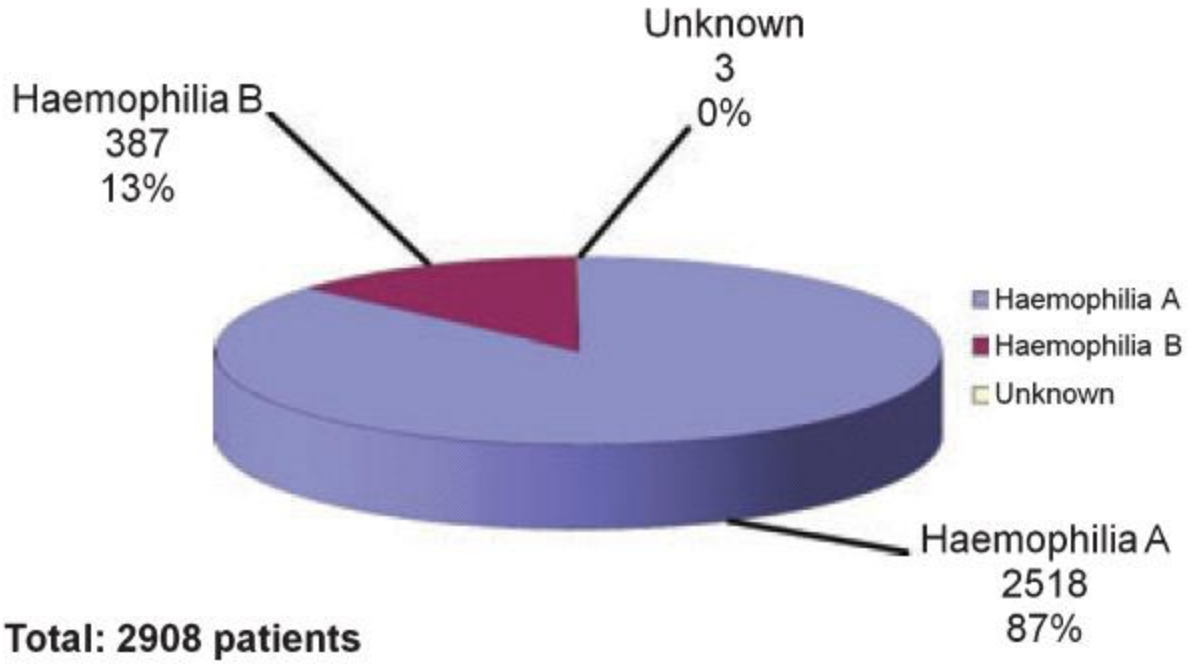


Fig. 1. Distribution by type of haemophilia.

Cada año se diagnostican en España entre 20 y 25 nuevos casos de hemofilia

HEMOFILIA A

Economic Impact

- One of the 8 most costly diseases
- Despite being low-volume, consumes over 30 times higher annual health expenditures than an "average" patient
- Annualized per patient costs can exceed $100,000 *just for Factor replacement*
- Multiple Indirect Cost Drive Economic Risk
  - Emergency costs associated with lack of immediate and/or appropriate treatment
  - Prolonged hospitalizations
  - Joint replacement surgery
  - Physical therapy to keep joints mobile

TRATAMIENTO

Objetivo: evitar la aparición de hemorragias graves y otras complicaciones

- **Concentrados de Factor VIII plasmático**

- **Factor VIII recombinante**

Avances tecnológicos (SEGURIDAD) pFVIII

Cribado serológico del plasma de los donantes

Doble inactivación viral (solvente/detergente + calor)

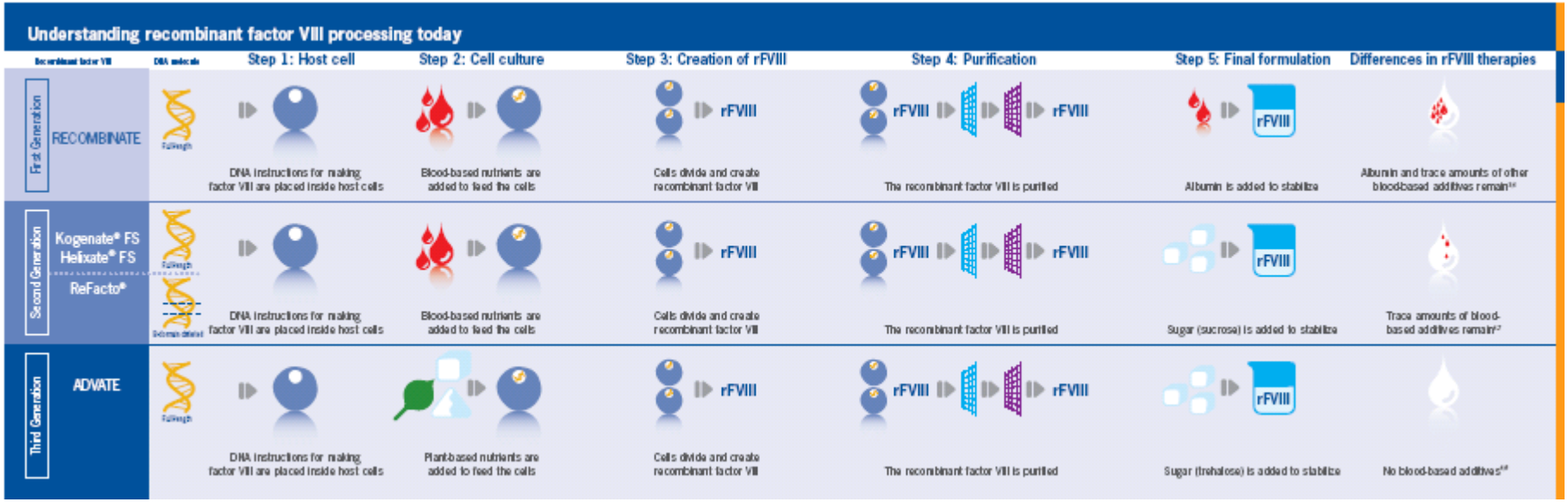
Purificación (métodos cromatográficos/inmunoafinidad)

- Permitir la eliminación de todos los virus, incluidos los virus sin cubierta.
- No generar neoantigenicidad en el producto tratado.
- No precisar la adición de materiales que posteriormente deban retirarse.
- Utilizar aditivos que no sean mutagénicos.
- No provocar pérdida de producto.
- Ser aplicables al final del proceso o a la proteína final.
- Ser adaptables a diferentes escalas de producción industrial.
- Ser rápidos y aplicables a muchos tipos de productos.
- Requerir controles sencillos.
- Ser económicos y de fácil aplicación.

Tabla 1: Criterios de optimización de los métodos de inactivación viral, según Drohan

rFVIII

Eliminación de proteínas exógenas



NATIONAL HEMOPHILIA FOUNDATION
www.hemophilia.org

MASAC Document #215
(Replaces Document #210)

MASAC RECOMMENDATIONS CONCERNING PRODUCTS LICENSED FOR THE TREATMENT OF HEMOPHILIA AND OTHER BLEEDING DISORDERS
(Revised November 2012)

1. Recombinant Factor VIII Concentrates

Recombinant (r) FVIII is produced by well-established hamster cell lines that have been transfected with the gene for human FVIII.(1,2) Two recombinant factor VIII products have the B domain deleted from the factor VIII gene before it is inserted into Chinese hamster ovary cells (3). First generation rFVIII contains animal and/or human plasma-derived proteins in the cell culture medium and in the final formulation vial. Second generation rFVIII contains animal or human plasma proteins in the medium but not in the final formulation, while third generation rFVIII does not contain any animal or human plasma-derived proteins in the culture medium or in the final formulation vial.

The risk of human viral contamination associated with recombinant FVIII is definitely much lower than for plasma-derived FVIII products. No seroconversions to HIV, HBV, or HCV have been reported with any of the currently available products; thus recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. (Table I.A.)

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2. Plasma-Derived Factor VIII Concentrates

Improved viral-depleting processes and donor screening practices have resulted in plasma-derived (pd) FVIII products that have greatly reduced risk for transmission of human immunodeficiency virus and hepatitis B and C. No seroconversions to HIV, HBV, or HCV have been reported with any of the pdFVIII products currently marketed in the United States, including products that are heated in aqueous solution (pasteurized), solvent-detergent treated, and/or immunoaffinity purified. Thus, each of these methods appears to have greatly reduced the risk of viral transmission compared with older methods of viral inactivation (4-6). There remains the *possibility* of HIV-1, HIV-2, or hepatitis B or C virus transmission with the use of currently marketed, viral-inactivated, plasma-derived products. The non-lipid enveloped viruses human parvovirus B19 and hepatitis A virus were also transmitted by pdFVIII (7-9); additional steps such as viral filtration have been added to reduce these risks as well. (Table I.B.)

7. Mannucci PM, Gdovin S, Gringeri A, et al. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with solvent and detergent to inactivate viruses. Ann Int Med 1994; 120:1-7.
8. Centers for Disease Control and Prevention. Hepatitis A among persons with hemophilia who received clotting factor concentrate - United States, September - December 1995. MMWR 1996; 45:29-32.
9. Azzi A, Ciappi S, Zakuyzewska K, et al. Human parvovirus B19 infection in hemophiliacs first infused with two high-purity, virally treated factor VIII concentrates. Am J Hematol 1992; 39:228-230.

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(Revised November 2012)

II. Recommendations to Manufacturers of Coagulation Products

A. We recommend continued vigilance in donor screening and donor testing at blood and plasma collection facilities.
   1. Plasma must not be collected in donor centers that draw from population groups in which there is a relatively high incidence of hepatitis and AIDS.
   2. Manufacturers should disclose the incidence of hepatitis and HIV infection at individual plasma collection centers. Maximum allowable viral marker rates for the donor population for anti-HCV, anti-HIV, and HBsAg should be established.
   3. Manufacturers should use only plasma that is collected by facilities qualified to receive the International Quality Plasma Program (IQPP) certification of the Plasma Protein Therapeutics Association (PPTA) and processed by fractionators certified by the QSEAL program of the PPTA in accordance with recommendations to hemophilia treatment centers (see "MASAC Recommendations on the IQPP and QSEAL Programs of the Plasma Protein Therapeutics Association," MASAC Document #139).
   4. Plasma should not be accepted for further processing until the donor has successfully passed at least two health history interviews and screening tests within a specified time period.
   5. All donations should be held for at least 60 days. If during this period the donor seroconverts and tests positive for a virus or is otherwise disqualified, the held donation should be destroyed.

15514 *REAL DECRETO 1088/2005, de 16 de septiembre, por el que se establecen los requisitos técnicos y condiciones mínimas de la hemodonación y de los centros y servicios de transfusión.*

C. *Donación autóloga y autotransfusión*

1. Exclusión permanente.

1.1 Enfermedad cardiaca grave, dependiendo de las circunstancias clínicas en el momento de la extracción.

1.2 Personas con antecedentes de:

a) Hepatitis B, excepto las personas que resulten negativas al antígeno de superficie de la hepatitis B (AgHBs), cuya inmunidad haya sido demostrada.
b) Marcadores positivos para el VHC.
c) Marcadores positivos para VIH- I/II.
d) Marcadores positivos para HTLV I/II.

2. Exclusión temporal.

2.1 Infección bacteriana activa.

1.10 Encefalopatías espongiformes transmisibles; enfermedad de Creutzfeldt-Jacob y variante de la enfermedad de Creutzfeldt-Jacob: personas con antecedentes familiares, o personas que hayan sido sometidas a trasplante de córnea o duramadre o que en el pasado hubieran recibido tratamiento con medicamentos derivados de glándula pituitaria humana. Quedan asimismo excluidas las personas con estancia superior a 12 meses en el Reino Unido durante el periodo 1980-1996.

1.11 Consumo de drogas: antecedente de consumo de drogas por vía intravenosa o intramuscular no prescritas, incluido tratamiento esteroideo u hormonal para aumento de la musculación.

1.12 Personas sometidas a xenotrasplantes.

1.13 Conducta sexual: exclusión de personas cuya conducta supone riesgo elevado de contraer enfermedades infecciosas graves transmisibles a través de la sangre y componentes sanguíneos.

1.14 Transfusiones: exclusión de personas con antecedentes de haber sido transfundidos en el Reino Unido o en países donde son endémicos: paludismo, sida, infección por HTLV y enfermedad de Chagas.

2.1.11 Virus del Nilo Occidental*: exclusión durante 28 días tras abandonar una zona en la que se detectan casos de transmisión a humanos.

2.2 Exposición al riesgo de contraer una infección transmisible por transfusión.

2.2.1 Exclusión durante seis meses (o durante cuatro meses, si la prueba de detección del virus de la hepatitis C mediante tecnología de amplificación genómica del ácido nucleico –NAT– resulta negativa) en caso de:

a) Endoscopia con instrumental flexible.
b) Salpicadura de sangre a mucosa o lesión con aguja.
c) Transfusión de componentes sanguíneos.
d) Trasplante de tejidos o células de origen humano.
e) Cirugía mayor.
f) Tatuaje o perforaciones de piel o mucosas («piercing»).
g) Acupuntura, salvo la practicada por un profesional cualificado con agujas estériles desechables.
h) Personas con riesgo debido a contacto doméstico directo o relación sexual con personas afectas de hepatitis B.

2.2.2 Personas cuya conducta o actividad sexual supone un riesgo elevado de contraer enfermedades infecciosas graves que puedan ser transmitidas por la sangre: tras el cese de la conducta de riesgo, exclusión durante un periodo determinado por la enfermedad en cuestión y por la disponibilidad de pruebas apropiadas en cada caso.

Blood Transfus 2010;8:288-291 DOI 10.2450/2010.0072-10

DEBATE

Plasma-derived versus recombinant factor VIII concentrates for the treatment of haemophilia A: plasma-derived is better

Pier Mannuccio Mannucci

Scientific Direction, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy

Thus, taking in account these clinical and experimental findings on inhibitor development, inhibitor eradication using plasma-derived VWF/FVIII products and also considering their lower costs and the high degree of safety reached now, I conclude that plasma-derived VWF/FVIII products should be strongly considered as an adequate therapeutic choice not only in patients already being treated with these products, but also in previously untreated or minimally treated children.

Haemophilia

Haemophilia (2011), 17, 179–184 DOI: 10.1111/j.1365-2516.2010.02431.x

COMMENTARY

A commentary on the differences in pharmacokinetics between recombinant and plasma-derived factor IX and their implications for dosing

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Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Summary. This commentary aims to summarize all aspects of the difference in pharmacokinetics (PK) between recombinant factor IX (rFIX) and plasma-derived factor IX (pdFIX) and their implications for dosing. PK data were compiled from 17 published studies. The average clearance (CL) of rFIX normally ranged between 7.5 and 9.1 mL h^{-1} kg^{-1}, whereas that of pdFIX was 3.8–5.4 mL h^{-1} kg^{-1}. The average terminal half-life was 18–24 h among all 72-h studies on rFIX, in contrast to (normally) 29–43 h for pdFIX. *In vivo* recovery was more variable. Judging from the pooled data, the typical recovery of rFIX is around two-third that of pdFIX. The difference in PK between rFIX and pdFIX is thus clear-cut and has implications for dosing. As estimated from the compiled data, the dose required to reach any peak level of FIX immediately after administration would be 1.5 times higher for rFIX than for pdFIX, most probably with considerable individual variation. Calculated doses for a patient on a twice weekly prophylactic treatment to achieve a predetermined trough FIX level depended markedly on CL and were about twice as high with rFIX as with pdFIX. In summary, conversion factors between rFIX and pdFIX of 1.5 for single doses and 2 for prophylactic dosing can tentatively be applied; however, the interindividual variance both in recovery and CL of rFIX and pdFIX and the unknown variance in ratios between these PK parameters call for careful monitoring if a switch of treatment is made.

Keywords: dose tailoring, factor IX, pharmacokinetics

Conversion factors between rFIX and pdFIX of 1.5 for single doses and 2 for prophylactic dosing can be applied

Haemophilia (2008), 14, 142–144 DOI: 10.1111/j.1365-2516.2007.01604.x

LETTER TO THE EDITOR

Factor VIII products and inhibitor development: concepts for revision of European regulatory guidelines

D. Treatment of Patients with Inhibitors to Factor VIII or IX

Inhibitor development is the most common and most severe complication of hemophilia treatment.

No está claro si el tipo de FVIII influye decisivamente en la aparición de inhibidores. Hay datos que sugieren una mayor incidencia con FVIII recombinante

La frecuencia de desarrollo de inhibidores parece comparable en PUP y PTP. Hay datos que sugieren que los pacientes naive pueden tener más riesgo.

Son necesarios grandes estudios observacionales post-autorización y registros internacionales con estandarización de criterios clínicos y analíticos

blood

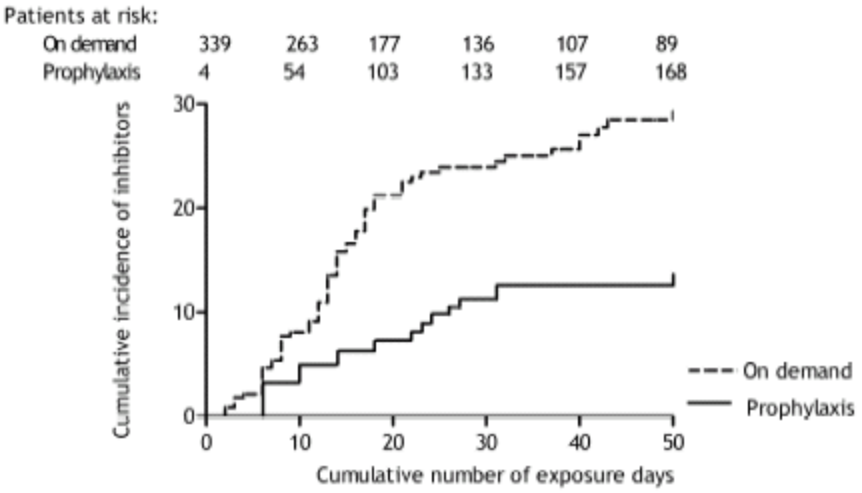
Prepublished online Feb 8, 2007;
doi:10.1182/blood-2006-11-056291

Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study

Samantha C. Gouw, Johanna G. van der Bom and H. Marijke van den Berg

FACTORES DE RIESGO

- **Intensidad del tratamiento inicial**
- **Tipo de tratamiento (profilaxis vs "a demanda").**



Pathophysiology of Haemostasis and Thrombosis

Pathophysiol Haemost Thromb 2002;32(suppl 1):29–32

Economic Impact of Treating Inhibitor Patients

Loretto Lacey

Lacey Solutions Ltd, Dublin, Ireland

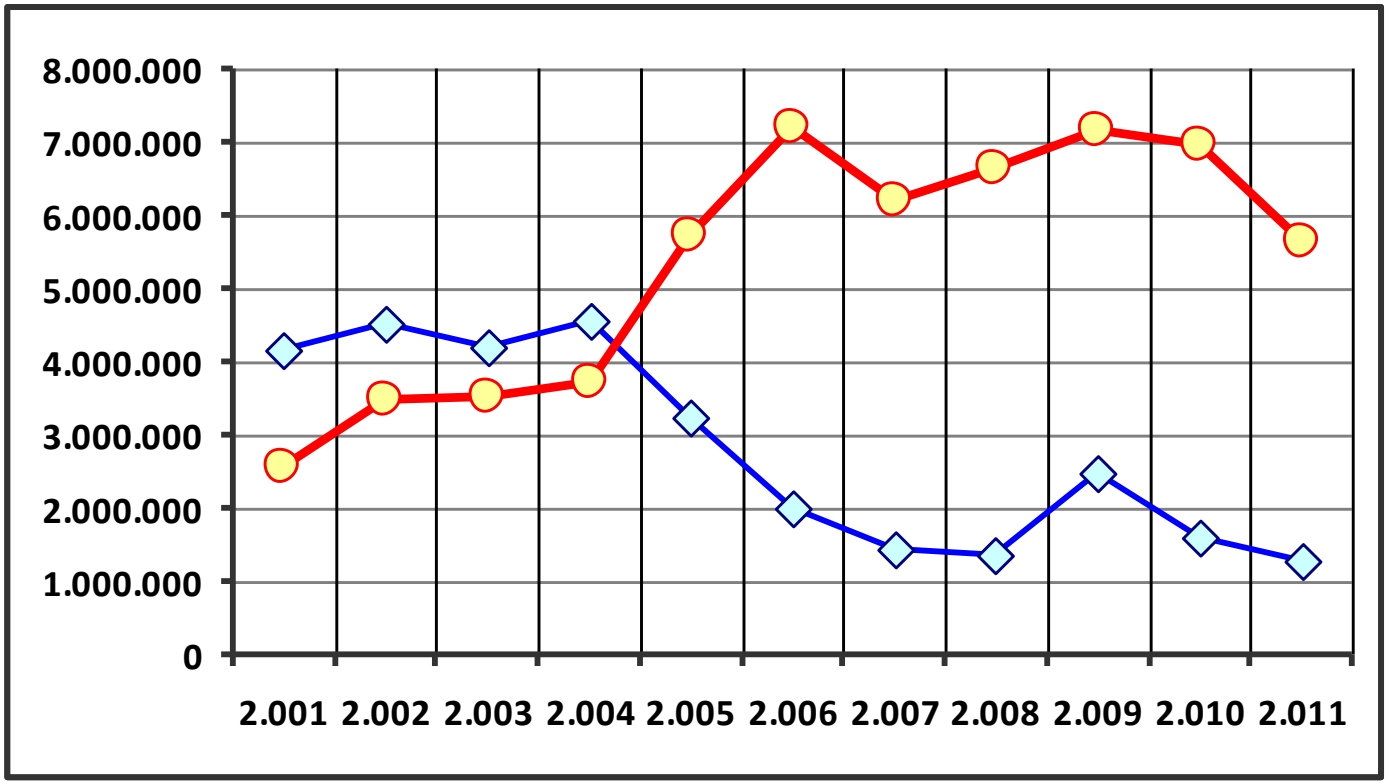
Table 4. Health care costs in Euro.

Resource	Cost/ patient-month (in euro)	% of total cost
Recombinant factor VIIa	8,491.9	47.3
Recombinant factor VIII	3,174.2	17.7
Human plasma-derived factor VIII	3,077.1	17.2
Activated prothrombin complex concentrate	2,982.0	16.6
Visits, surgeries and hospitalizations	209.9	1.2
Total	17,935.1	100

ANALISIS FARMACOECONOMICO

Hospital U Virgen del Rocío

UI



2011: **5,1 % del gasto total del hospital**

Motivos

- Aumento progresivo en la utilización de FVIII recombinante
- Fluctuaciones en el consumo de factores por paciente (episodios hemorrágicos)
- Incremento en los costes de adquisición
- Desarrollo de inhibidores (tto. inmunotolerancia)
- Implementación de estrategias de contención del gasto

Componentes del coste por paciente:

Severidad de la enfermedad (déficit de FVIII)

Frecuencia y gravedad de los episodios hemorrágicos

Modalidad de tratamiento:

- **Profilaxis (niños y adolescentes)** →

rFVIII 180.000 €/año

- **Tratamiento a demanda (adultos)** →

pFVIII / rFVIII 90.000 €/año

1.650 hemofílicos tratados con FVIII en España

Coste rFVIII: 0,6 €/ UI

Coste pFVIII: 0,4 €/ UI

HUVR

Año 2006: 9.199.750 UI (+3%): 5.721.132 € (+45%)

Cambio “masivo” de pFVIII a rFVIII

Contención del incremento del gasto

Evitar el paso a rFVIII en pacientes que vienen siendo tratados con pFVIII durante años:

- **No se obtendrá mayor beneficio en el control de las hemorragias**
- **No hay evidencia de que disminuya la incidencia de transmisión de enfermedades infecciosas**
- **Mayor riesgo de desarrollo de inhibidores (¿?)**
- **Se incrementa el gasto un 50% (30.000 €/año por paciente)**

Contención del incremento del gasto

Utilización preferente de pFVIII procedente del fraccionamiento de los excedentes de plasma humano

BOCM BOLETÍN OFICIAL DE LA COMUNIDAD DE MADRID

B.O.C.M. Núm. 196 VIERNES 17 DE AGOSTO DE 2012 Pág. 79

I. COMUNIDAD DE MADRID

D) Anuncios

Consejería de Sanidad

SERVICIO MADRILEÑO DE SALUD

21 *RESOLUCIÓN de 1 de agosto de 2012, de la Viceconsejería de Asistencia Sanitaria, por la que se hace pública la convocatoria de licitación por procedimiento abierto, mediante criterio precio, del contrato de servicios denominado "Fraccionamiento industrial de plasma humano proveniente del Servicio Madrileño de Salud para la obtención de derivados plasmáticos de uso terapéutico".*

COSTE: aprox. 50% respecto al preparado comercial

HUVR: el gasto en pFIX en 2012 ha descendido un 40%

Contención del incremento del gasto

Consideración de los distintos preparados de Factor VIIIr como EQUIVALENTES TERAPÉUTICOS

Haemophilia (2009), 1–4 DOI: 10.1111/j.1365-2516.2009.02079.x

ORIGINAL ARTICLE

Efficacy assessment of a new clotting factor concentrate in haemophilia A patients, including prophylactic treatment

Annual FVIII consumption per kg and annual number of joint bleeds before and after switching to the new albumin-free recombinant factor concentrate were similar in all patients. In conclusion, rAHF-PFM is equally effective as other clotting factor concentrates for prophylactic treatment in severe haemophilia.

(rAHF-PFM, Advate®)

Haemophilia (2009), 1–6 DOI: 10.1111/j.1365-2516.2009.02071.x

ORIGINAL ARTICLE

Pharmacokinetics, coagulation factor consumption and clinical efficacy in patients being switched from full-length FVIII treatment to B-domain-deleted r-FVIII and back to full-length FVIII

No significant difference was detected between the half-life measurements during the switch from FL FVIII (T/2 median 9.15 h, range 6.4–22) to BDD rFVIII (T/2 median 9.7, range 4.7–16.8) and back to FL FVIII (T/2 median 9.0, range 5.0–19.5). There was no significant difference in coagulation factor usage (BDD rFVIII median 4803 IU kg^{-1} - $year^{-1}$, range 659–11 304; FL FVIII median 5349, range 1691–10 146), nor bleeds. Eleven received BDD rFVIII to cover surgical procedures, with no reports of excess bleeding. Thirty-three patients received significant exposure to BDD rFVIII and one developed a low titre inhibitor. BDD rFVIII was found to be equivalent to other FVIII products in terms of pharmacokinetics, clinical efficacy and safety in this study group.

Haemophilia (2009), 15, 869–880 DOI: 10.1111/j.1365-2516.2009.02027.x

ORIGINAL ARTICLE *Clinical haemophilia*

Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full-length recombinant factor VIII

A double-blind, randomized, pharmacokinetic (PK) cross-over study, utilizing a central laboratory assay (one-stage (OS)) for both drug potency assignment and plasma FVIII-activity measurements, demonstrated that BDDrFVIII was PK-equivalent to a full-length rFVIII.

Contención del incremento del gasto

Consideración de los distintos preparados de Factor VIIIr como EQUIVALENTES TERAPÉUTICOS

- Concurso Centralizado de Determinación de Tipo (año 2007)
- Procedimiento Negociado a nivel local

	ANEXO V	
LOTE	MEDICAMENTO	PML (EUROS)
95	Factor VIII recombinante de 2ª o 3ª generación, inyectable 1000 UI.	680,000

Procedimiento Negociado en HUVR:

Oferta adjudicada: 595 € (-11,5% respecto a PVL)

Erradicación de Inhibidores: Inducción de Inmunotolerancia (ITI)

. Immune tolerance induction (ITI), through the regular infusion of coagulation factor concentrates over a time period ranging from 1 to more than 24 months, is successful in about 75% of high responders. Among the issues of ITI treatment that are still open, the choice of the product to use is one of the most difficult. In fact, common practice is to start with the same product that induced the inhibitory response, but recent findings indicated that plasma-derived products containing large amounts of von Willebrand factor (VWF) can play a positive role

Erradicación de Inhibidores: Inducción de Inmunotolerancia (ITI)

Pauta: 200 UI/Kg/sem

Costes asociados:

r-FVIII: 500.000 €/año

VWF-FVIII : 300.000 €/año

Haemophilia (2007), 13 (Suppl. 5), 73–77

VWF/FVIII concentrates in high-risk immunotolerance: the RESIST study

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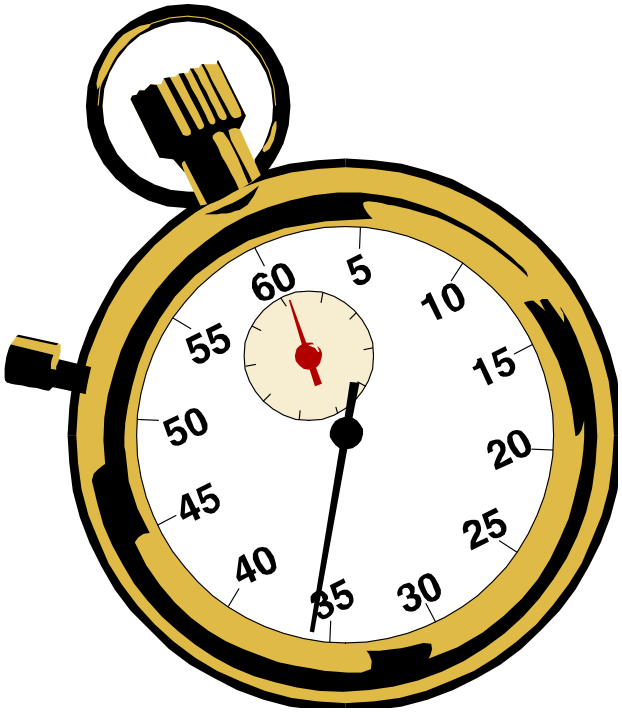
CONCLUSIONES

La hemofilia A representa un importante impacto sanitario y presupuestario (alto coste, tratamiento indefinido)

El tratamiento con pFVIII es la opción más costo-efectiva (pacientes tratados previamente)

La consideración de los distintos rFVIII como E.T. (pacientes de inicio) puede mejorar la eficiencia

La utilización de VWF/FVIII en los tratamientos de ITI tiene un importante impacto en los costes



Gracias!