

The role of plasma products in the treatment of haemophilia today

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Inhibitors remain the greatest challenge to haemophilia care today

Mark Skinner, WFH President, Jan 2006:

“Today, both plasma-derived and recombinant products enjoy a robust record of safety.”

„We need a better understanding of the risk for and incidence of inhibitor development.“

„Historically, we have **primarily considered pathogen risks** such as HIV, hepatitis, and variant Creutzfeldt-Jakob disease (vCJD).

In the future, we must define risk more broadly. The risk of developing an inhibitor, a problem faced by 20-30 per cent of patients with severe hemophilia A, and the risk of an unstable or inadequate supply of treatment products are **also of vital importance.**“

PRESIDENT'S MESSAGE

Assessing and communicating risk with hemophilia treatment products

Mark Skinner
WFH President



A key WFH objective is the adequate provision of safe, efficacious, and affordable replacement therapy as part of a sustainable national hemophilia program. In previous columns, I have described WFH efforts to improve the affordability of treatment products. However, even if affordable, any therapy must first be safe and efficacious.

The WFH continuously monitors the safety of the treatment products and advocates for their improvement. Historically, we have primarily considered pathogen risks such as HIV, hepatitis, and variant Creutzfeldt-Jakob disease (vCJD). In the future, we must define risk more broadly. The risk of developing an inhibitor, a problem faced by 20-30 per cent of patients with severe hemophilia A, and the risk of an unstable or inadequate supply of treatment products are also of vital importance.

and needless patient stigmatization must be balanced against the dangers of underreaction and patient harm. In these cases, counseling, competent explanation, and clear information (acknowledging uncertainty) are essential.

Optimally, both patient organizations and leading clinicians would be consulted in the development of any risk communication with patients. To be meaningful, consultation should be conducted early and made part of the risk assessment process. Even with preliminary risk assessments, understanding the current thinking of public health officials can be quite helpful in preparing patients for the eventual publication of a formal risk assessment.

Many social and economic factors influence the level of risk we as individual patients are willing to accept in our treatment. These individual decisions are often very subjective and not scientifically based. Thus, organizations such as the WFH have become vital partners in the safety network. We fulfil this role through the many product safety, education, and advocacy programs of the WFH.

An additional complication is the global nature of the clotting factor business. We may be faced with a range of risk assessments performed by different countries with limited consensus between them. Efforts between national regulatory bodies to coordinate risk assessments as accurately as possible would reduce patient confusion and anxiety.

It is now well established that safety is a shared responsibility of many different organizations, not simply regulatory bodies. Patients have an absolute right to be informed and consulted during any risk assessment.

To ensure equal treatment, complete openness in communication is required for both domestic and overseas audiences. This is particularly true when the same products are subject to differing assessments, as has been the case with vCJD.

It is important to recognize that efforts to assess risk arise frequently in situations where there is limited scientific knowledge or certainty. As patients, in such circumstances we value the basic principle when in doubt, decision makers should err on the side of precaution. To achieve trust in this process, transparency and inclusion should be the foundation of any risk assessment.

We will all be better served if we adhere to the basic principles of inclusion and transparency in any risk assessment or risk communication. ■

Once risk is assessed, effective communication is the next challenge. Where uncertainty exists, communicating risk to patients require a delicate balance. The need to prevent overreaction

HEMOPHILIAWORLD • JANUARY 2006

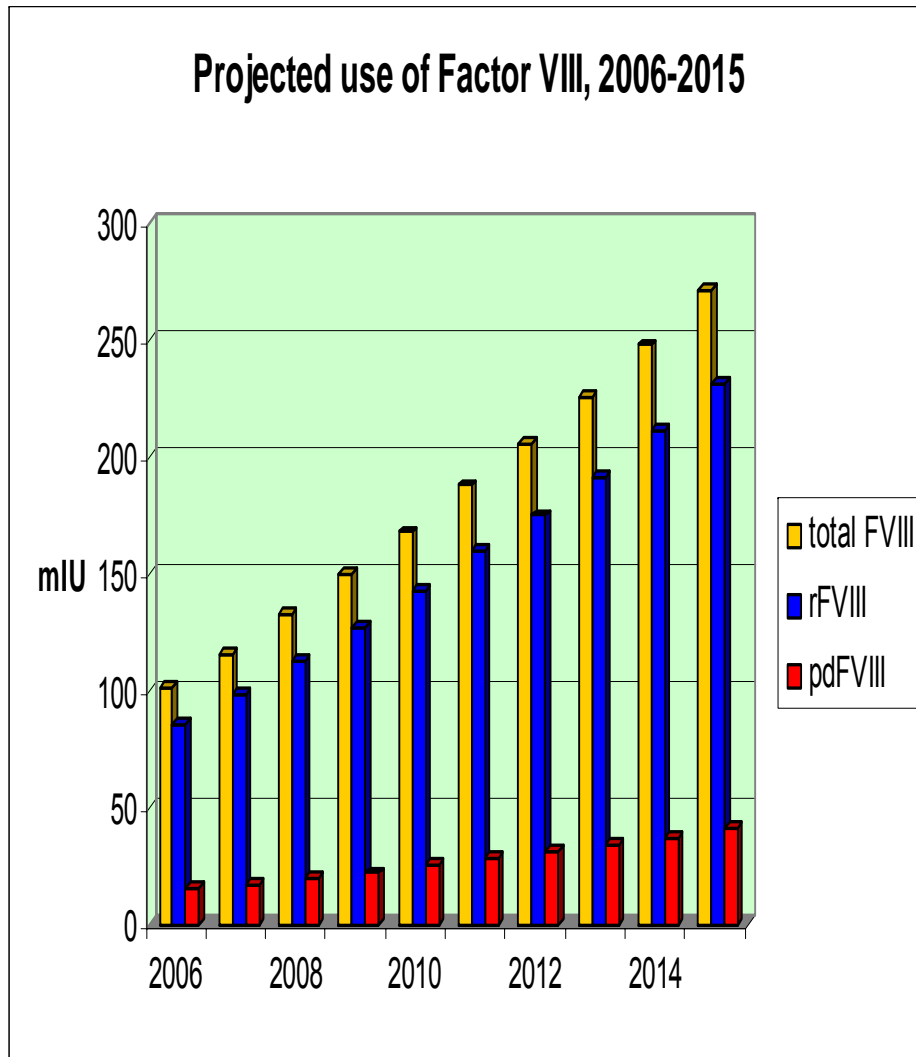
Severe Haemophilia A in Australia

(ABDR data 2007)

- Product using HA patients = 572
- Hepatitis C (>18 years) = 90%
- HIV = 25%
- Inhibitor rate 8.5%
- Prophylaxis 31% of adults
- Factor use 128,000IU per year (per person)

- Adults: rVIII = 94.2%
pdVIII only = 3.3%

- Children: rFVIII = 94%
pdFVIII = 2.9%



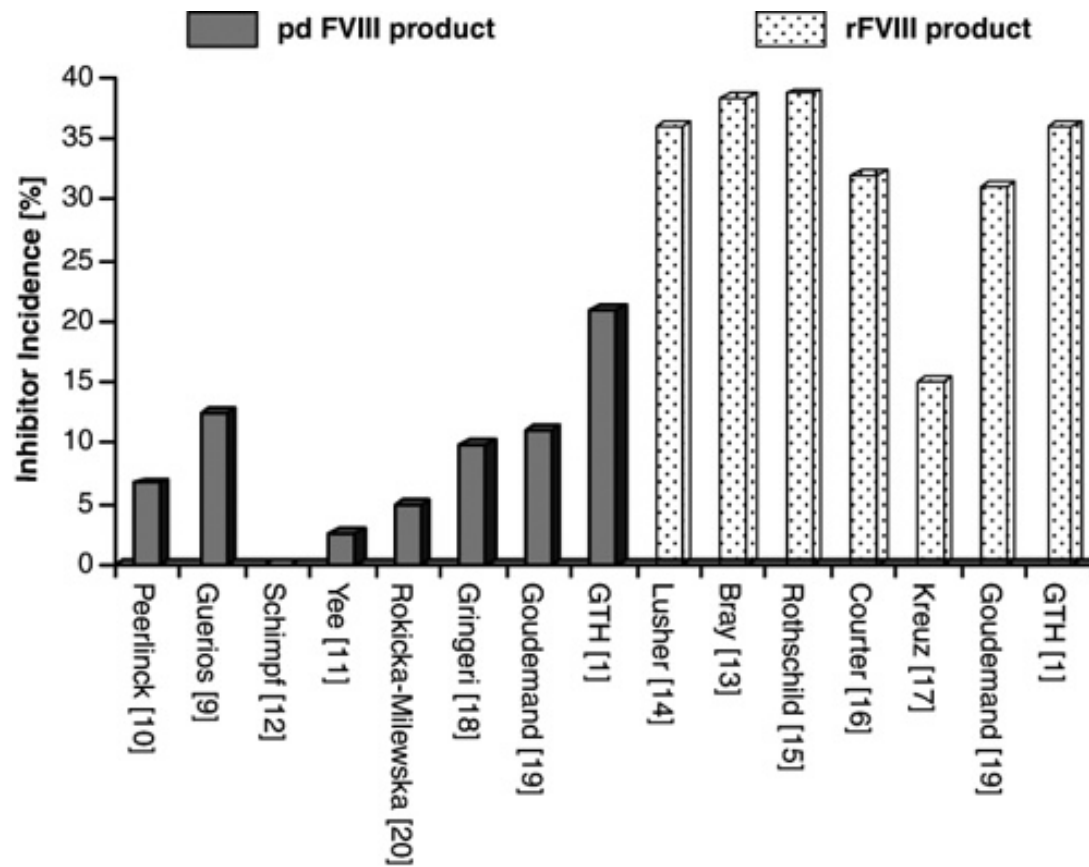
Factors which might lead to increased demand for FVIII

1. Population increase
2. Prophylaxis
3. Extended life expectancy
4. Surgery
 - cardiac; oncology; orthopaedic
5. Increased body mass (obesity in haemophilia)
6. Inhibitor frequency (plasma product preference ?)

Rate of inhibitor development pdFVIII vs rFVIII

Wight and Paisley Haemophilia 2003;9:418-435.

Single pdFVIII concentrates inhibitor rate 0-12% vs 36-38% rFVIII



Ettingshausen et al.

Haemophilia 2006;12:102-6

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 Claeysens, Yves Laurian, Thierry Calvez, and the members of the FVIII-LFB and Recombinant FVIII study groups

Table 1. Characteristics of the cohorts

	FVIII-LFB; n = 62	Recombinant FVIII*; n = 86
Follow-up		
Period	1988-1999	1991-2002
Median time to follow-up, mo (range)	48.4 (1.0-127.5)	24.6 (0.3-84.4)
Mean per patient of interval between 2 inhibitor tests		
Median CEDs (25th-75th percentile)	5.4 (4.0-7.4)	5.2 (3.5-7.4)
Patients with average interval no higher than 10 CEDs (%)	51 (82)	72 (84)
Median, mo (25th-75th percentile)	4.4 (3.3-6.3)	3.2 (2.4-4.5)
Exposure‡		
Median CEDs (range)	108 (1-544)	38 (3-655)
Patients with at least 50 CEDs (%)	40 (65)	36 (42)
Patients with at least 100 CEDs (%)	32 (52)	25 (29)
Genetic cofactors, no. (%)§		
High-risk mutations	36 (58)	44 (51)
Other mutations	23 (37)	35 (41)
Nonwhite	7 (11)	17 (20)
Family history of hemophilia and inhibitor	9 (15)	6 (7)
Family history of hemophilia without inhibitor	23 (37)	23 (27)
Environmental cofactors, no. (%)§		
Age at first infusion		
Younger than 6 months	17 (27)	18 (21)
6 to 11 months	21 (34)	29 (34)
End point (%)		
Patients with inhibitors, 0.6 BU or more	7 (11)	27 (31)
No. of high inhibitors, more than 5 BU	3 (5)	13 (15)
No. of high inhibitors, more than 5 BU and/or ITI	4 (6)	19 (22)

Treated with single product

No switch

VWF content 0.2-0.4 IU/ 1 IU FVII

Full length recombinant

No difference in RF's

Blood 2006; 107:46-51.

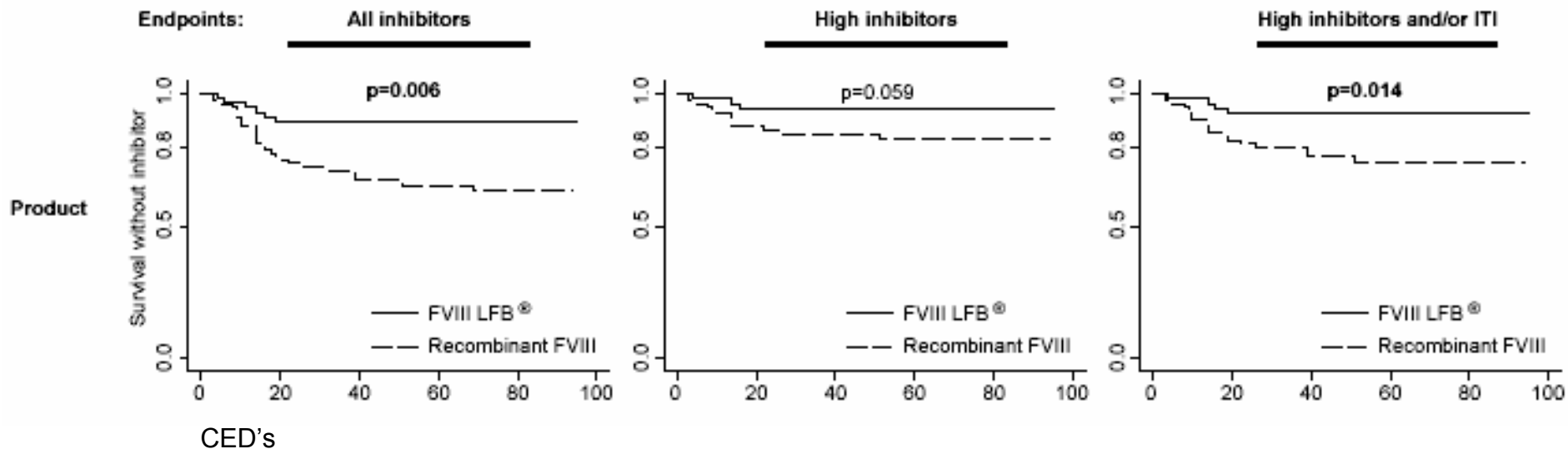


Table 3. Multivariate analysis (Cox model) of inhibitor incidence according to risk factors

Product	All inhibitors				High inhibitors				High inhibitors and/or ITI			
	CII (%)	RRa	95% CI	P	CII* (%)	RRa	95% CI	P	CII (%)	RRa	95% CI	P
FVIII-LFB	10.3	1.0	—	.049	5.2	1.0	—	.157	6.9	1.0	—	.045
Recombinant FVIII*	32.3	2.4	1.0-5.8		15.0	2.6	0.7-9.6		23.7	3.2	1.0-9.7	

J Goudemand et al, Blood 2006; 107: 46-51.

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

Samantha C. Gouw,^{1,2} Johanna G. van der Bom,³ Günter Auerswald,⁴ Carmen Escuriola Ettinghausen,⁵ Ulf Tedgård,⁶ and H. Marijke van den Berg,¹ for the CANAL Study group

¹Van Creveldkliniek, University Medical Center Utrecht, the Netherlands; ²Department of Pediatrics, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands; ³Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; ⁴Prof Hess-Kinderklinik, Zentrum für Kinderheilkunde und Jugendmedizin, Bremen, Germany; ⁵Centre of Pediatrics III, Department of Hematology, Oncology and Haemostaseology, Johann-Wolfgang-Goethe University Hospital, Frankfurt AM Main, Germany; ⁶Department of Pediatrics, University of Lund, University Hospital, Malmö, Sweden

316 PUP's from 14 centres

SHA < 2%

> 50 CED's

> High VWF product > 0.02 IU
VWF_{Ag} per IU FVIII

Multiple products

Of 135 pdFVIII – 33 low VWF

No assoc between low vs high found

36% of pdFVIII switched to
recombinant median 5 CED (vs 3%)

Less distinct calendar difference so ?
Product selection on pt characteristic

Blood 2007; 109: 4693-4697.

Table 2. Risk of inhibitor development according to type of factor VIII product

	NED	All clinically relevant inhibitor development				High-titer inhibitor development*			
		Crude		Adjusted		Crude		Adjusted	
		RR (CI)	P	RR (CI)	P	RR (CI)	P	RR (CI)	P
Recombinant	8493	1.0		1.0		1.0		1.0	
Plasma-derived	4425	0.8 (0.5-1.3)	.34	0.7 (0.4-1.1)	.14	0.9 (0.5-1.5)	.72	0.8 (0.4-1.3)	.33
Recombinant	8493	1.0		1.0		1.0		1.0	
Plasma-derived									
Low VWF content†	1272	0.3 (0.1-1.1)	.07	0.4 (0.1-1.1)	.08	0.3 (0.1-1.2)	.09	0.3 (0.1-1.3)	.11
High VWF content†	3153	1.0 (0.6-1.6)	.91	0.8 (0.5-1.4)	.45	1.1 (0.7-2.0)	.61	0.9 (0.5-1.6)	.79
Kogenate	4267	1.0		1.0		1.0		1.0	
Kogenate Bayer	378	1.1 (0.2-4.5)	.94	1.2 (0.3-5.4)	.79	1.5 (0.3-6.5)	.60	1.6 (0.3-7.3)	.55
Recombinate	1639	1.1 (0.5-2.3)	.75	1.0 (0.5-2.1)	.99	1.4 (0.6-3.1)	.39	1.2 (0.5-2.7)	.70
Refacto	2209	1.4 (0.8-2.6)	.24	1.6 (0.9-3.2)	.14	1.5 (0.7-3.0)	.30	1.4 (0.6-3.1)	.38

Adjusted for baseline factor VIII activity level, ethnicity, factor VIII gene mutation type, age at first exposure, duration between exposure days, dose of factor VIII, and regular prophylaxis.

Gouw et al. Blood 2007; 109: 4693-4697.

Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A

E. A. CHALMERS,* S. A. BROWN,† D. KEELING,‡ R. LIESNER,§ M. RICHARDS,¶ D. STIRLING,** A. THOMAS,†† V. VIDLER,‡‡ M. D. WILLIAMS§§ and D. YOUNG* ON BEHALF OF THE PAEDIATRIC WORKING PARTY OF UKHCDO

*Royal Hospital for Sick Children, Glasgow; †Royal Free Hospital, London; ‡Oxford Radcliffe Hospital, Oxford; §Great Ormond Street Hospital, London; ¶St James' Hospital, Leeds; **Edinburgh Royal Infirmary, Edinburgh; ††Royal Hospital for Sick Children, Edinburgh; ‡‡Sheffield Children's Hospital, Sheffield; and §§Birmingham Children's Hospital, Birmingham. UK

348 PUP's with > 50 CED from 1987-2003 in 8 UK HTC's

43% initially received pdFVIII

(no switch data)

Long interval between inhibitor testing

No product data re VWF content etc

Inhibitors 14% pdFVIII vs 27% rFVIII

(p=0.009) with RR 2.24 (CI 1.24-4.04)

Multivariate analysis RR 1.83 (CI 0.9-3.72)

HR 10% vs 15% (p=0.17)

Haemophilia 2007; 13: 149-155.

Summary of inhibitor risk

	French	CANAL	UK
All inhibitors	23%	26%	20%
HR	10%	21%	10%
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	all inhibitors		
pdFVIII	RR 1.0	1.0	1.0
rFVIII	2.4 (1.0-5.8)	1.4 (0.9-2.5)	1.8 (0.9-3.7)
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	high responding		
pdFVIII	1.0	1.0	
rFVIII	2.6 (0.7-9.6)	1.25 (0.8-2.5)	
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ITI in Frankfurt

Data from Dr Kreuz ISTH 2007

	<i>Type of concentrate</i>	<i>Complete ITI</i>	<i>Success rate</i>
1979-93		[n/n]	[%]
Patients	pd (FVIII-vWF)	19/21	91%
Since 1993			
Patients n=16	pd (FVIII-vWF)	2/2	100%
	hp FVIII	4/14	29%
n=10	Changed to pd FVIII-vWF	8/10	80%
total		14/16	88%

[Kreuz et al.; Haematologica, 2001]

**Data from Dr Kreuz ISTH 2007
- Haemophilia Centres Bonn and Bremen -**

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

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

**Salvage ITI with
change of high purity FVIII concentrates without VWF
to FVIII containing VWF* (1993-2001) at Frankfurt HTC**

High responders (>5 BU) n=13	median	range
Age at first ED (years)	1.0	0.1-50
Number of EDs until inhibitor (n)	13	4-100
Maximum inhibitor titre (BU)	97	8-287
Time until change of concentrate (months)	3.3	1.4-20
Time until complete success (months)	17	5-36

Complete success in 10 of 13 patients

Use of FVIII/VWF in inhibitor patients as salvage 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	VWF/FVIII complex concentrate	8 (median)	7/8 complete success 1 partial success
Gringeri et al, 2006	4	4	200 IU/kg BW	VWF-FVIII complex concentrate		3/4 complete success

Use of FVIII/VWF for ITI in inhibitor patients with bad prognostic factors*

Author	No of pts [n]	HR [n]	Therapy regimen	Product	Therapy duration [months]	Outcome
Gringeri et al., 2006	13	13	200 IU/kg BW	VWF-FVIII complex concentrate	18 (median) 4-30	7/13 complete success 5 partial success 1 failure / drop out
Portuguese experience 2006	7	6	200 IU/kg BW	VWF-FVIII complex concentrate	7 (mean) 3-22	6/7 complete success

*Delayed onset of ITI of >2y, or Age >6 years, or Inhibitor peak >200 BU, or Inhibitor titre > 10 BU when ITI started

INVITED REVIEW

Immune tolerance therapy for factor VIII inhibitors: moving from empiricism to an evidence-based approach

D. DIMICHELE

Weill Medical College of Cornell University, New York, NY, USA

Study	Product	Dose	Success rate
<i>VWF-containing factor VIII (F VIII)</i>			
Brackmann 1996 [2]	Haemate P®	High	71–88 %
Orsini 2005 [26]	Factane®	Various	87 %
<i>High purity plasma-derived/recombinant F VIII</i>			
Smith 1999 [4]	Monoclonal/ recombinant	High	100 %
Rocino 2006 [5]	Monoclonal/ recombinant	Intermediate	83 %
<i>Recombinant F VIII</i>			
Lusher 1994 [28]	Kogenate®	High	63 %
Bray 1994 [29]	Recombinate®	High	50 %
Battle 1999 [30]	Kogenate®	High	77 %
Courter 2001 [31]	Refacto®	High	81 %
Barnes 2006 [27]	Kogenate®	Various	76 %
Rocino 2006 [22]	Various	Intermediate/ high	73 %

- NAITR reported a higher success rate with ITI using pdFVIII (73%) cf rFVIII (51%)

(DiMichele D, et al. [Abstract] Blood 2000;96:266a)


- Guidelines from UKHDO, European Consensus Panel and International Consensus Panel don't not feel there is adequate evidence to influence product choice
- RESIST study : ITI naive patients randomised to 200U/kg/d of either pdFVIII or rFVIII

The international ObsITI – study programme


Observational study in Immune Tolerance Induction

Principal Investigators: Wolfhart Kreuz, C. Escuriola-Ettingshausen
 University Hospital of Frankfurt, Germany

Co-Investigators: Erik Berntorp, Jan Astermark
 University Clinics of Malmö, Sweden



OBSITI
 Johann Wolfgang Goethe University
 Dept. of Hematology and Oncology
 Frankfurt / Main, Germany



Title	A Survey on the Success Rate of Inhibitor Elimination Using Controlled (High Dose) Immune Tolerance Induction (ITI)
Indication	Immune Tolerance Induction (ITI)
Design	International open-label, uncontrolled, non-interventional, multi-centre <i>observational</i> program,

Patient inclusion criteria

- Severe or moderate haemophilia A patients with FVIII-inhibitors and **at least one poor prognostic factor** for ITI:
 - age >7y
 - inhibitor >2y after inhibitor diagnosis
 - historical peak inhibitor titre of >200 BU
 - titre >10 BU at start of ITI
 - earlier ITI-failure or interruption
- patients with no concomitant immunosuppressive or experimental treatment

Octanate in ObsITI – treatment regimen

According to the high-dose (HD) / Bonn protocol:

- High responders with ≥ 5 BU at start of ITI:
100-150 IU FVIII/kg every 12 hours
- Low responders with < 5 BU at start of ITI:
50-100 IU FVIII/kg per day or every other day
- In case of acute bleeding during ITI:
90-120 μg FVIIa/kg every 2 hours until the hemorrhagic syndrome resolves

Interim results of the ongoing ITI cases

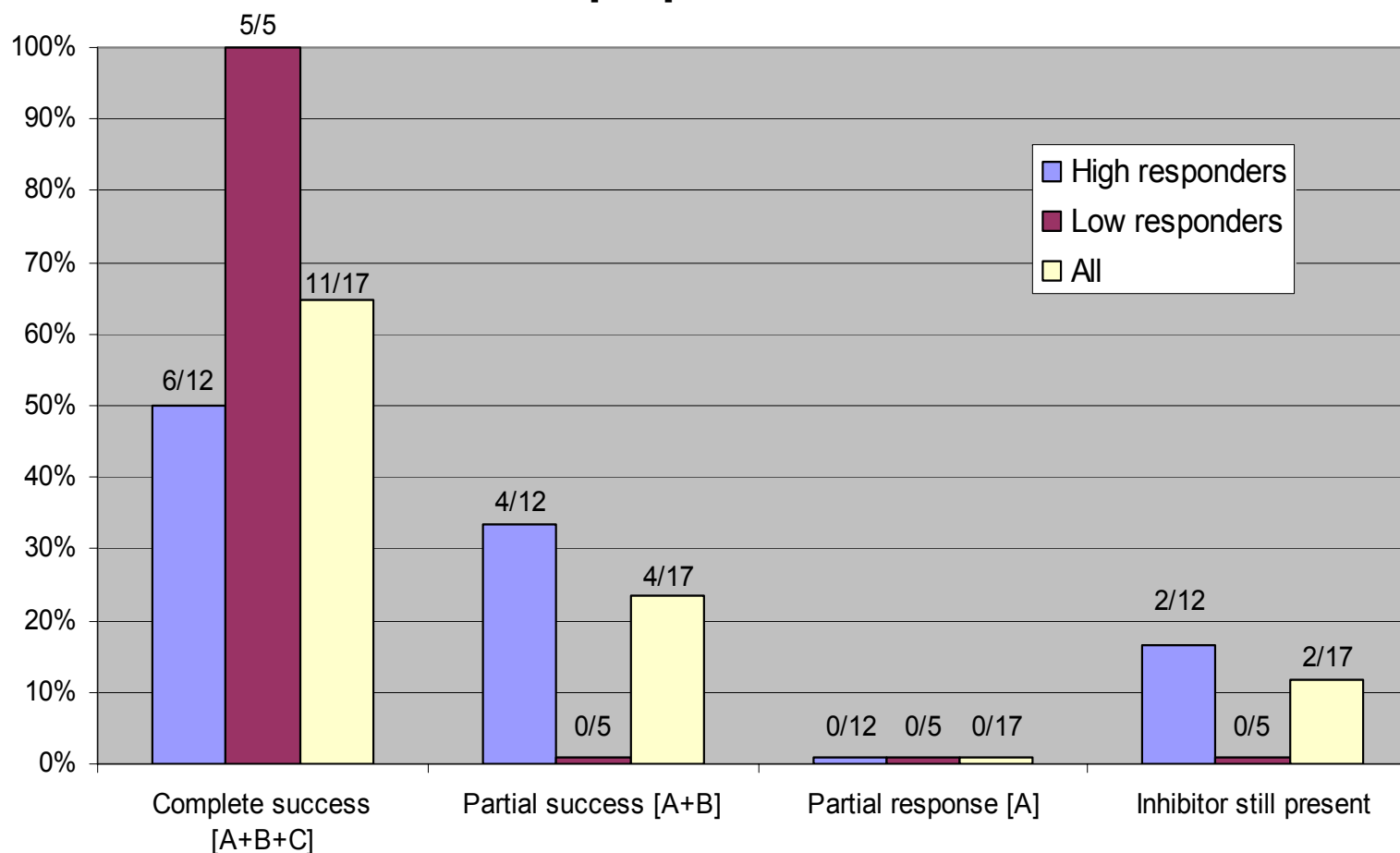
ITI success milestones:

A=Inhibitor titre <0.6 BU

B=Normalized FVIII recovery

C=Normalized FVIII half-life

- Overall interim ITI-success rate for partial [A+B] or complete [A+B+C] success is 88.3%.
- 10 of 12 high responders (83%), and 5 of 5 low responders (100%) show complete [A+B+C] or partial [A+B] success.

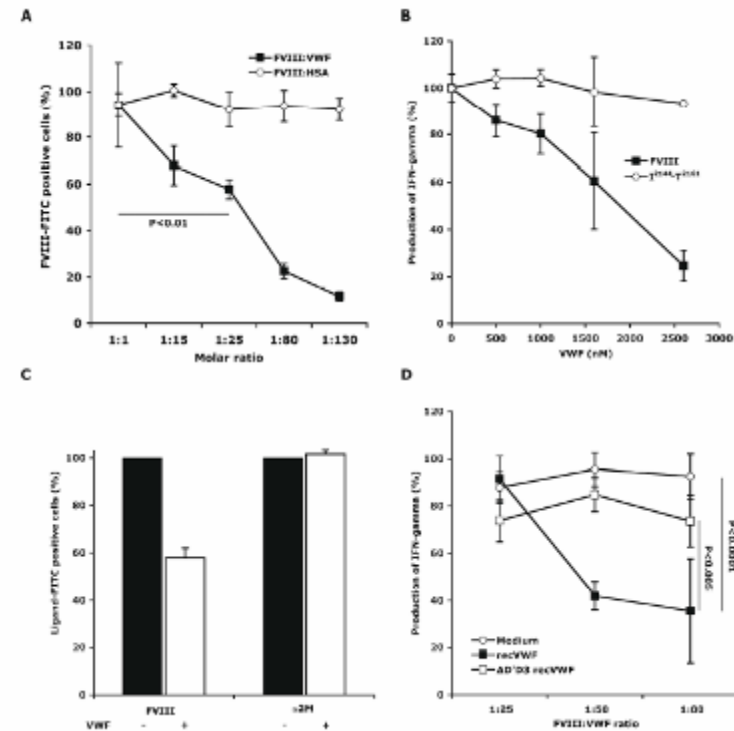
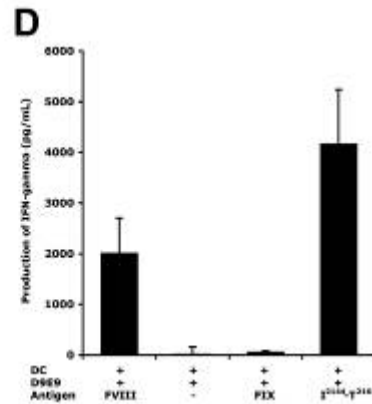
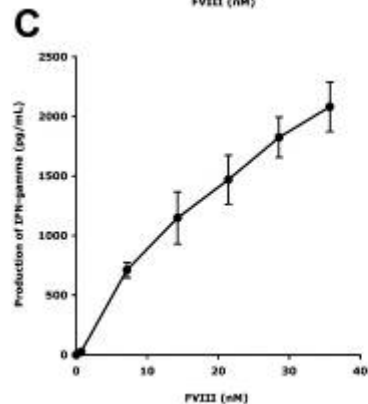
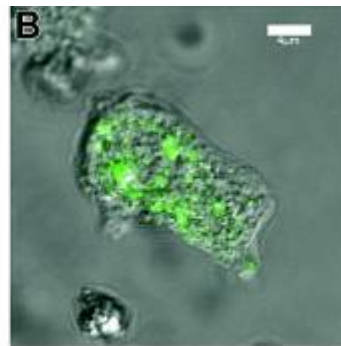
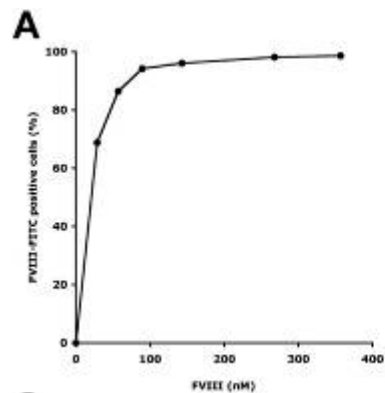


VWF protects FVIII from endocytosis by dendritic cells and subsequent presentation to immune effectors

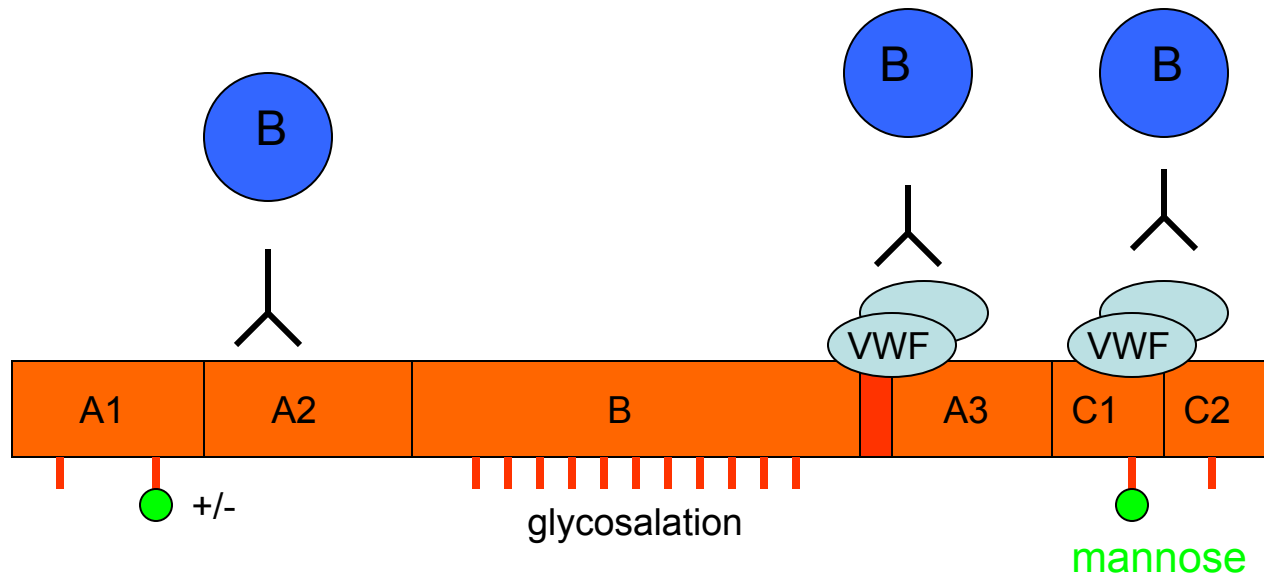
Dasgupta S and Lacroix-Desmazes s.

Blood 2007; 109: 610-612.

1. Dendritic cells take up FVIII (A and B)
2. Causing activation of T cells (C and D)

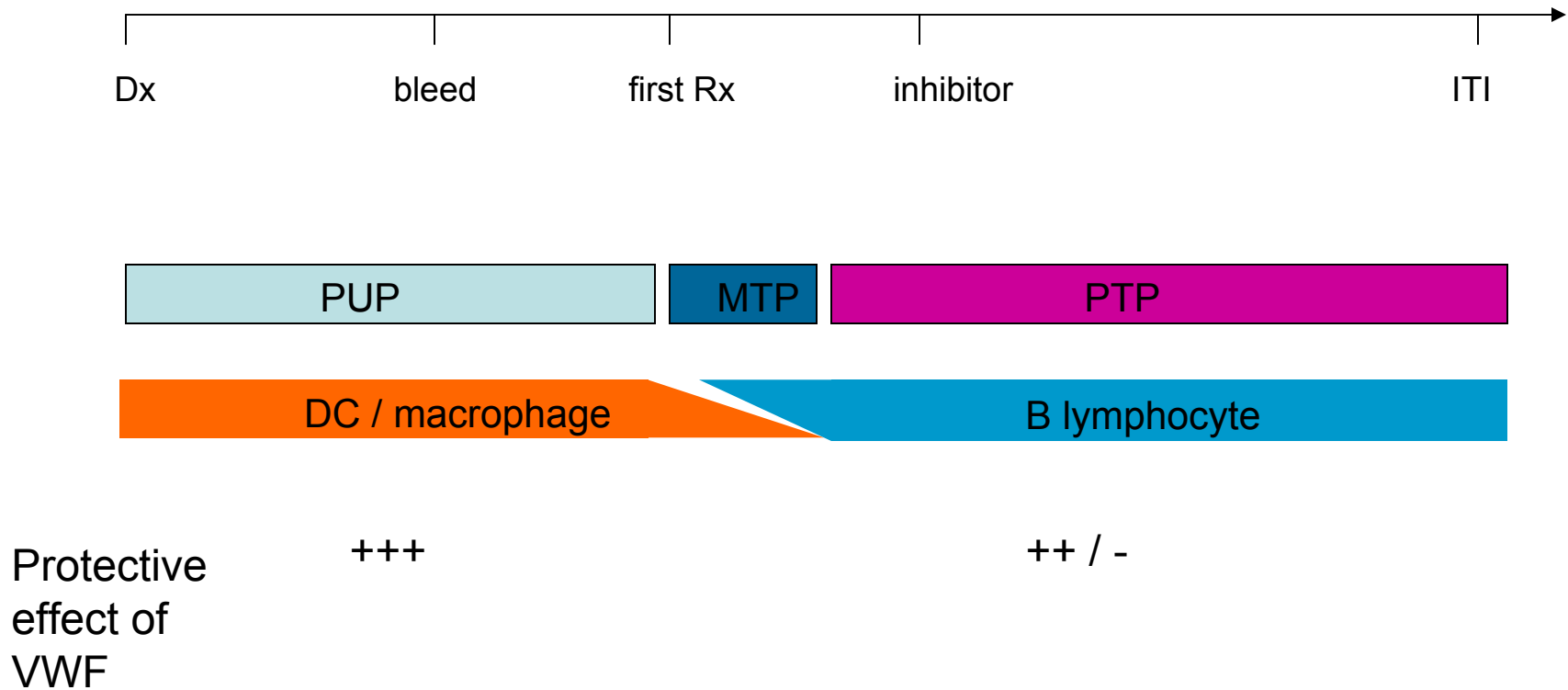


3. DC uptake is blocked by VWF (40%) (A and C)
4. Which also blocks T cell activation (B)
5. And this is dependent upon FVIII:VWF binding with no inhibition shown using a VWF mutant that doesn't bind FVIII (D)



- the DC receptor responsible for FVIII uptake is the macrophage-mannose receptor
- unusually mannose sugars are present on the C1 and variably A1 domains
- VWF light chain binding protects against uptake
- also VWF can block antibodies directed against C1 (and A3) formed by previously sensitized B cells acting as APC's (Suzuki TH 1996)
- but protective effect depends upon affinity of Ab vs VWF

Protective effect of VWF



Effect of factor VIII concentrate on leucocyte cytokine receptor expression and tolerance induction

Haemophilia (2006), 12, 133–139

DOI: 10.1111/j.1365-2516.2006.01200.x

Effect of factor VIII concentrate on leucocyte cytokine receptor expression *in vitro*: relevance to inhibitor formation and tolerance induction

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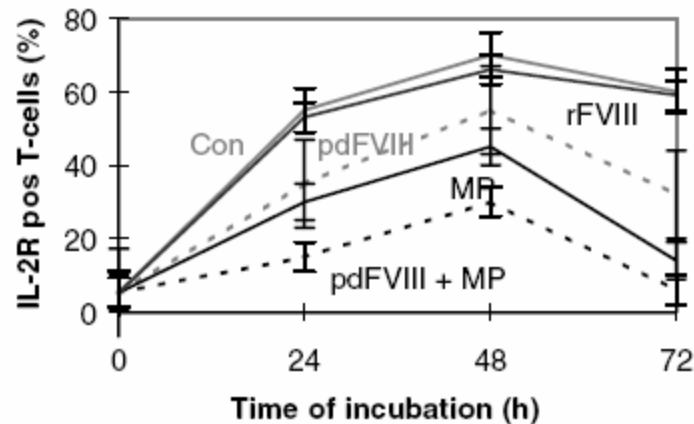


Fig. 1. Graph showing the effect of 2.5 IU mL^{-1} of plasma-derived factor VIII (pdFVIII), 2.5 IU mL^{-1} recombinant FVIII (rFVIII), 10^{-7} M prednisolone (P) and a combination of 2.5 IU mL^{-1} of pdFVIII and 10^{-7} P on the upregulation of the interleukin-2 α R (CD25) on T cells following stimulation of whole blood with $10 \mu\text{g mL}^{-1}$ phytohaemagglutinin (PHA) (mean \pm SEM of five experiments). Upregulation of CD25 on T cells was significantly inhibited in the presence of 2.5 IU mL^{-1} of pdFVIII and 10^{-7} of P ($P < 0.05$) at all time points. The inhibition of upregulation of T cell CD25 in the presence of both pdFVIII and P was additive. No change in cytokine receptor upregulation was noted in the presence of 2.5 IU of rFVIII ($P > 0.05$ for all time points).

- T cell and monocyte cytokines are inhibited in the presence of pdFVIII
- up regulation of T cell, monocyte as well as B cell receptors (including memory CD40/CD40L) was inhibited by pdFVIII cf rFVIII
- The use of pdFVIII, particularly the more inhibitory batches, may be more suitable than rFVIII for tolerance induction protocols."

[Greg Hodge et al., *Haemophilia* 2006]

The beneficial role of VWF in ITI

- In vitro observations -



Impact on thrombin generation of different inhibitor reactivities with commercial factor VIII concentrates

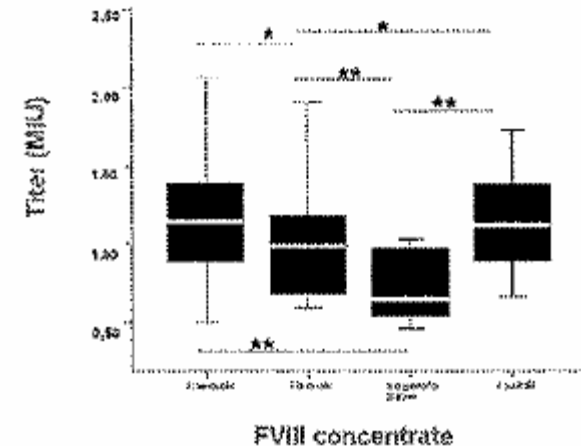


Gian Luca Salvagno ¹, Jan Astermark ², Maj Ekman ², Massimo Franchini ³, Gian Cesare Guidi ¹, Giuseppe Lippi ¹, Giovanni Poli ¹, Erik Berntorp ²

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1- Aim

To further substantiate the hemostatic role of variation in inhibitor reactivity with different FVIII concentrates we compared inhibitor titers from 11 plasmas against a panel of FVIII concentrates and correlated titer with capacity to inhibit thrombin generation elicited by each concentrate using a thrombin generation assay.



Inhibitor titers needed to inhibit 50% thrombin generation were lowest for non-VWF-containing concentrates

“This study confirms results from previous studies regarding variation of inhibitor reactivity against different concentrates and further shows that VWF-containing concentrates generate more thrombin than Hemofil M and Kogenate Bayer in the presence of FVIII inhibitors.”

The thrombin generation assay results add further evidence for the role of VWF in the treatment of patients with inhibitors.

Can we risk profile patients to help guide product choice ?

Concept provided by J Oldenburg

Good Risk Factors

Genetic Background

- ✓ Negative family history
- ✓ Non-severe haemophilia
- ✓ Caucasian origin
- ✓ Missense mutation
- ✓ IL10 134 negative
- ✓ TNF alpha A2 negative
- ✓ CTLA4-318 T positive

Environmental

- ✓ Early prophylaxis
- ✓ Absence of danger signals
- ✓ Type of concentrate:
VWF-stabilized FVIII

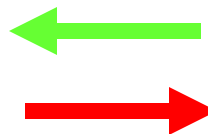
Bad Risk Factors

Genetic Background

- Positive family history
- Severe haemophilia
- African origin
- Null mutation
- IL10 134 positive
- TNF alpha A2 positive
- CTLA4-318 T negative

Environmental

- Early event-based treatment
- Intensive treatment
- Continuous infusion
- Danger signals
- Type of concentrate: no VWF



Thanks for your attention