Il bambino con emofilia

corso di formazione ad alta specializzazione sulla gestione del bambino con emofilia

Padova 13-14 maggio 2016

L' immunotolleranza

Antonio Coppola

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TREATING HEMOPHILIA IN THE III MILLENNIUM*

FVIII on demand or prophylaxis

Effective and safe standard of care

Preserved Joint status

Satisfactory QoL

Prolonged life exepctancy

Manco-Johnson et al, 2007
Gringeri et al, 2011
Gringeri et al 2001
Tagliaferri et al, 2010

...but

INHIBITOR

↑ bleeding risk
↓ efficacy of treatment

↑ morbidity
↑ severity of arthropathy

Worse QoL

Higher mortality ?

Strikingly high impact on costs

Gringeri et al, 2003; UKHCDO, 2004
Scalone et al, 2006; Morfini et al, 2007
Knight, 2009; Di Minno, 2010

*in high-income countries

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Manco-Johnson et al, 2007
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L'induzione di immuno-tolleranza (ITI) consente di eradicare o ridurre la produzione di alloanticorpi inibitori anti-FVIII, **ripristinando la terapia sostitutiva standard, efficace e sicura, con concentrati di FVIII**

Esposizione ripetuta e protratta nel tempo (a dosi più o meno elevate) **all'antigene** verso il quale gli anticorpi sono diretti

DOI: 10.1111/j.1365-2516.2010.02237.x

Brackmann and Gormsen (*Lancet* 1977; ii: 933): Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder

- 1.5-yr child; severe bleeding in the right shoulder, arm and chest; inh titer >500 BU/ml
- Treatment with high-dose FVIII (100 IU/Kg every 12 hours) and prothrombin complex concentrate.
- Control of bleeding.
- Three weeks later: inh 40 BU/ml.
- Treatment (aPCC 50 IU/Kg bid) in other patients. Despite initial inhibitor boosting in some, decrease of inhibitor titer was recorded in all patients and continuation of treatment resulted in inhibitor eradication.

Different regimens, same results…

ITI protocol	FVIII dose and associated treatment	Success rate (%)	Median time to success, months	Comments
Bonn protocol (high-dose regimen)*	FVIII 100–150 iu/kg every 12 h until inhibitor <1 BU, then FVIII 150 iu/kg until normalization of FVIII recovery and half-life.	92–100	14	Very demanding for patients. High cost
Malmö protocol (high-dose regimen + immune modulation)†	FVIII continuous infusion targeting plasma levels >30 iu/dl until negative inhibitor titre, then 60–90 iu/kg weekly + cyclophosphamide (i.v. 12–15 mg/kg days 1–2, 2–3 mg/kg orally days 3–10) + i.v. immunoglobulins 2·5–5 g/kg day 1, 0·4 g/kg days 4–8. Preliminary protein A sepharose immunoadsorption if initial inhibitor titre >10 BU.	59–82	1	Rapid response and cost-saving but need for hospitalization and concerns regarding the use of cyclophosphamide in children
Dutch protocol (low-dose regimen)‡	Neutralizing dose (25–50 iu/kg twice daily, 1–2 weeks), then tolerizing dose (50–75 iu/kg weekly)	61–88	1–12§	Less demanding for patients and cost-saving
Other low or intermediate dose protocols	Ewing *et al*, 1988: 50 iu/kg/d	67	2¶	Developed for improving cost-effectiveness of treatment
	Kucharski *et al*, 1996: 50 iu/kg/week	45	10	
	Unuvar *et al*, 2000: 50–100 iu/kg/d	57	6	
	Rocino *et al*, 2001: 100 iu/kg/d	75	8	

94

32

24

~60

*Brackmann *et al* (1996) and Oldenburg *et al* (1999); activated prothrombin complex concentrates (aPCC) 40–60 iu/kg every 12 h was included until 1996.

†Nilsson *et al* (1988) and Freiburghaus *et al* (1999).

‡van Leeuwen *et al* (1986) and Mauser-Bunschoten *et al* (1995).

Reported patients

Coppola et al, Br J Haematol, 2010

Registri ITI: pazienti

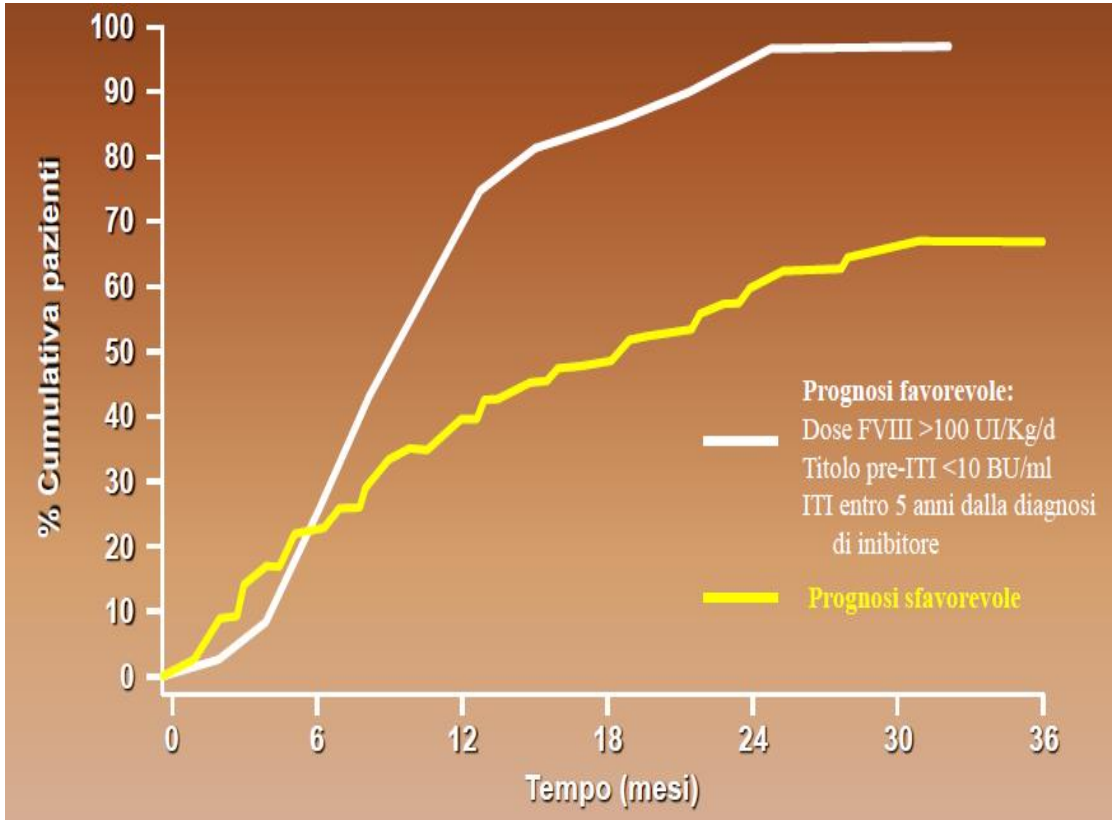
Registro	Età all'ITI anni
Internazionale IITR Mariani 2001, **n=314**	13 (1-64) (mediana)
Nordamericano NAITR DiMichele 2009, **n=164**	9.3 (0.1-64) (media)
Tedesco GITR Lenk 2000, **n=126**	14.1 (media) (2/3 'young children')
Spagnolo Haya 2001, **n=37**	7 (0.6-57) (mediana)
PROFIT Coppola 2009, **n=103**	5.6 (0.3-58.5) (mediana)

Profilo prognostico favorevole

Registro Internazionale ITI

Fattori associati a successo	p
• Titolo pre-ITI <10 BU/ml	.03
• Picco storico <200 BU/ml	.01
• Tempo tra ITI e diagnosi di inibitore < 5 anni	.0001
• Dose FVIII > 100 UI/Kg	.001
• Età < 20 anni	. 005

Mariani & Kroner, Haematologica 2001



Peak historical titer < 200 BU/ml
Pre-ITI titer > 10 BU/ml
ITI < 5 yrs since inh diagnosis

Definizione di
'good-risk patients'

DiMichele et al, Haemophilia 2007

ITI clinical experience and research

Successful treatment of hemophilia a inhibitor patients with an induced immunotolerance

Brackmann & Gormsen, Lancet 1977, 2: 933.

National and International Registries

IITR
NAITR
GITR

n = 1

Randomized trials

1980 1990 2000 2010

Cohort studies

Bonn protocol
Malmö protocol
Dutch protocol
Low/intermediate dose protocols

Plenary paper Blood, 2012:119(6)1335-1344

The principal results of the International Immune Tolerance Study: a randomized dose comparison

Charles R. M. Hay[1] and Donna M. DiMichele,[2] on behalf of the International Immune Tolerance Study

[1]Department of Haematology, Manchester University, Manchester Royal Infirmary, Manchester, United Kingdom; and [2]Department of Pediatrics, Weill Cornell Medical College, New York, NY

Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B (Review)

Athale AH, Marcucci M, Iorio A

THE COCHRANE COLLABORATION®

2014

Authors' conclusions

We did not find any randomised controlled trial-based comparison of immune tolerance induction with alternate treatment schemes (i.e. bypassing agents for bleeding only). In a single randomised trial, there were no significant differences in the immune tolerance induction success rate between different dosing regimens, which may have been due to imprecision of the estimate. There is low-quality evidence to suggest that high-dose immune tolerance induction may induce tolerance more quickly which is associated with fewer bleeding complications. The choice of immune tolerance induction regimen should be considered individually for each case, until further research provides additional evidence.

ITI: the first choice of treatment in inhibitor patients

Grade B
Level IIb

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

GUIDELINES

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

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

able cost–efficacy ratio. Every patient with high-responding inhibitors should undergo, as early as possible an ITI treatment [1,5,24–28] (grade B

The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation

Br J Haematol 2006; 133:591-605

Charles R. M. Hay, S. Brown, P. W. Collins, D. M. Keeling and R. Liesner

Immune Tolerance Induction is recommended for patients with severe congenital haemophilia A and a confirmed FVIII or FIX inhibitor and should be considered as early as possible after the presence of an inhibitor has been confirmed (grade B recommendation, level of evidence IIB).

Haemophilia (2006), 12, 363–371 DOI: 10.1111/j.1365-2516.2006.01296.x

Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors

J. ASTERMARK,* M. MORADO,† A. ROCINO,‡ H. M. VAN DEN BERG§, M. VON DEPKA¶, A. GRINGERI,** L. MANTOVANI,†† R. P. GARRIDO,‡‡ M. SCHIAVONI,§§ A. VILLAR,† and J. WINDYGA¶¶ ON BEHALF OF THE EHTSB[1]

1. Children and adults with high-responding inhibitors (>5 BU mL^{-1}) should undergo ITI as soon as possible after inhibitor development,

Haemophilia (2007), 13 (Suppl. 1), 1–22

International workshop on immune tolerance induction: consensus recommendations[1]

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

immune tolerance induction (ITI) is usually attempted to eliminate high-responding (anamnestic) FVIII inhibitors of recent onset and restore normal factor pharmacokinetics [14]. ITI may also be performed,

SPECIAL ARTICLE

European Association for Haemophilia and associated disorders (EHAD)

European principles of haemophilia care

B. T. COLVIN,* J. ASTERMARK,† K. FISCHER,‡ A. GRINGERI,§ R. LASSILA,¶ W. SCHRAMM,** A. THOMAS†† and J. INGERSLEV‡‡ FOR THE INTER DISCIPLINARY WORKING GROUP

The management of patients with haemophilia and inhibitors is based on:

- timely diagnosis of inhibitor development and thorough follow-up;
- eradication of inhibitory activity;
- treatment of bleeding events;
- prevention of bleeding during surgery and
- prophylaxis of haemophilic arthropathy.

Eradication of the inhibitor in patients with haemophilia represents the main goal of treatment because it allows replacement therapy with standard clotting factor concentrates, which is the therapy with the most favourable cost-efficacy ratio [4]. Inhibitor eradication has been demonstrated to be achievable in three quarters of patients through ITT, based on regular infusions of high doses of clotting factor concentrates. Both children and adults with high-responding inhibitors (>5 BU mL^{-1}) should therefore undergo ITT as soon as possible after inhibitor development.

Haemophilia (2008), 14, 361–374

WFH GUIDELINES

Guidelines for the management of hemophilia

A. SRIVASTAVA,* A. K. BREWER,† E. P. MAUSER-BUNSCHOTEN,‡ N. S. KEY,§ S. KITCHEN,¶ A. LLINAS,** C. A. LUDLAM,†† J. N. MAHLANGU,‡‡ K. MULDER,§§ M. C. POON¶¶ and A. STREET***; TREATMENT GUIDELINES WORKING GROUP ON BEHALF OF THE WORLD FEDERATION OF HEMOPHILIA

Haemophilia (2013), 19, e1–e47

Immune tolerance induction

1. In patients with severe hemophilia A, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy. (Level 2)

The most recent recommendations

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

British Journal of Haematology, 2013, **160**, 153–170

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]

Irrespective of age and inhibitor titer

- Immune toleration induction is recommended for patients with severe haemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (Grade 1B).

US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors

Haemophilia (2015), **21**, 559–567

L. A. VALENTINO,* C. L. KEMPTON,†¶ R. KRUSE-JARRES,‡ P. MATHEW,§ S. L. MEEKS¶ and U. M. REISS** ON BEHALF OF THE INTERNATIONAL IMMUNE TOLERANCE INDUCTION STUDY INVESTIGATORS

1. Children with severe haemophilia A and persistent inhibitors >5 BU mL^{-1} (confirmed on ≥1 repeat measurement) with a peak historical inhibitor titre <200 BU mL^{-1} and other good-risk characteristics (Table 2) should receive ITI (Grade 1A) [2].
2. Children with severe haemophilia A and inhibitors >5 BU mL^{-1} (confirmed on ≥1 repeat measurement) with a peak historical inhibitor titre >200 BU mL^{-1}, regardless of poor-risk characteristics (Table 2), should receive ITI (1A) [12–15]. Higher doses are needed, and consideration should be given to initiating ITI with a VWF-containing product (2C) [42]
3. Adults with severe haemophilia A and inhibitors >5 BU mL^{-1} (confirmed on ≥1 repeat measurement), regardless of inhibitor duration, should be considered for ITI (2C), particularly those with frequent bleeding or a poor response to bypass therapy (1C) [12–15,43,44].

Blood Transfusion 2014;12:575-98

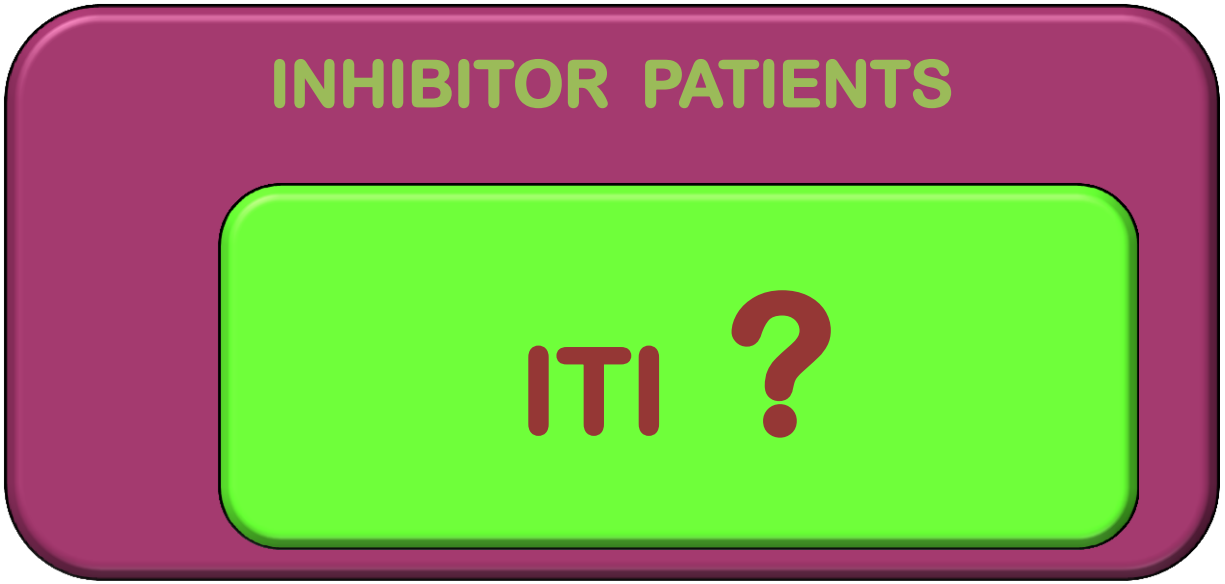
RECOMMENDATION

Principles of treatment and update of recommendations for the management of haemophilia and congenital bleeding disorders in Italy

Angiola Rocino[1], Antonio Coppola[2], Massimo Franchini[3], Giancarlo Castaman[4,5], Cristina Santoro[6], Ezio Zanon[7], Elena Santagostino[8], Massimo Morfini[9] on behalf of the Italian Association of Haemophilia Centres (AICE) Working Party (see appendix 1)

treatment[138,139]. ITI is recommended in all patients with severe haemophilia A and high-responding inhibitors by the WFH guidelines[8], the European principles of haemophilia care[9], international guidelines and expert panels[76-78,136] and is largely adopted in Italian HTCs[11]. This approach should also be considered in patients with persistent low-responding inhibitors, interfering with standard-dose FVIII prophylaxis or on-demand treatment[76,77]. The main candidates for ITI are children with recent onset high-responding inhibitors in whom early eradication can provide an optimal cost-utility ratio in a long-term perspective[140]. To this purpose, ITI

How many inhibitor patients do undergo ITI ?



- Literature provides data mostly on treated patients
- NAITR: 188 / 518 (36%) inhibitor patients (1992-1999)
  DiMichele & Kroner, Thromb Haemost 2002
- PROFIT: 88 / 149 (59%) inhibitor patients (1996-2010)
  - 65 / 74 children < 14 yrs (88%)
  - 23 / 75 patients > 14 yrs (31%)

Coppola et al, Blood Transfusion 2011

When to start ITI ?

Wait until inhibitor titer < 10 BU (level II b)

- wait is usually short (median 5.5 mo°)
- close surveillance of inh titer
- avoid FVIII exposure (anamnesis): rFVIIa, consider prophylaxis*
- even lower titers^

°good risk patients, Hay & Di Michele, 2012
*Santagostino et al, 2012, Valentino 2015

^ DiMichele et al, 2002; Hay et al, 2006; Coppola et al, 2009

International workshop on immune tolerance induction: consensus recommendations[1]

Haemophilia (2007), **13** (Suppl. 1), 1–22

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

When to start ITI ?

Start regardless of inh titer > 10 BU (level IV)

- **Persisting inh titer > 10 BU**
  > 1 – 2 yrs (lower success rates when ITI started > 5 yrs since inh diagnosis)*
- **Severe / life or limb- threatening bleeding**

*Mariani & Kroner, 1999

International workshop on immune tolerance induction: consensus recommendations[1]

Haemophilia (2007), **13** (Suppl. 1), 1–22

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

When to start ITI ?

- Immune toleration induction should be started as soon as possible after the inhibitor has been confirmed and when the titre is <10 BU/ml (Grade 1B).
- If the inhibitor titre is >10 BU/ml at diagnosis, the start of ITI should be deferred until it has fallen below 10 BU/ml (Grade 1B). If this has not happened after 1 year, consideration should be given to commencing ITI (Grade 2C).

When should ITI be started?.

1. ITI should be started as soon as possible (see points 2 and 3 below) when a high-titre inhibitor ≥5 to ≤10 BU mL^{-1} is detected and confirmed on ≥1 repeat measurement (1C) [12–15].
2. In patients with a peak inhibitor titre >10 BU mL^{-1}, we recommend postponing ITI until the titre drops to ≤10 BU mL^{-1} (1C) [12–15].
3. In patients with a peak inhibitor titre >10 BU mL^{-1} who experience serious or life-threatening bleeding or have frequent mild to moderate bleeding and are being considered for bypassing agent prophylaxis, an earlier start to ITI is favoured to avoid the morbidity associated with ongoing bleeding (1C) [12,13,46].

ORIGINAL ARTICLE *Clinical haemophilia*

Prompt immune tolerance induction at inhibitor diagnosis regardless of titre may increase overall success in haemophilia A complicated by inhibitors: experience of two US centres

Haemophilia (2015), 21, 365–373

C. NAKAR,* M. J. MANCO-JOHNSON,† A. LAIL,‡ S. DONFIELD,‡ J. MAAHS,* Y. CHONG,* T. BLADES† and A. SHAPIRO*

**The Indiana Hemophilia and Thrombosis Center (IHTC), Indianapolis, IN; †The University of Colorado Hemophilia & Thrombosis Center (UCHTC), Aurora, CO; and ‡Rho, Inc., Chapel Hill, NC, USA*

Table 2. ITI outcome

		All		HRI		
				Time interval from detection to ITI start		
Group	All	LRI*	HRI†	≤1 m	>1–6 m	>6 m
N (%)	58 (100)	19 (33)	39 (67)	23 (59)	5 (13)	11 (28)
Success, *N* (%)	51 (88)	19 (100)	32¶ (82)	22§ (96)	3§ (60)	7§ (64)
Failure, *N* (%)	7 (12)		7 (18)	1 (4)	2 (40)	4 (36)

	HRI ≤1 m	
Group	Pre-ITI <10 BU	Pre-ITI ≥10 BU
N (%)	10 (43)	13 (57)
Success, *N* (%)	9 (90)	13§ (100)
Failure, *N* (%)	1 (10)	

Fattori prognostici di successo nei Registri ITI

Variabile	IITR	NAITR	GITR	SITR	PROFIT
Successo (%)	50.9	63*	76*	63.4	52
Età all'ITI (range)	13 (1-64) (mediana)	9 (0.1-64) (media)	14 (media)	7 (0.6- 57) (mediana)	6 (0.3-58.5) (mediana)
Età al trattamento	.005 .008	.06	.55	n.s.	n.s.
Intervallo diagnosi inibitore - inizio ITI	.0001 -	.4	.85	n.s.	n.s.
Picco storico inibitore	.01 .04	.05	.0012	.02	.007 .56
Titolo pre-ITI (<10 BU/ml)	.03 .04	.005	n.r.	.03	<0.001
Picco inibitore durante ITI	n.r.	.0001	n.r.	n.r.	<0.001
Dose FVIII	alta .001 .03	bassa .01^	n.r.°	bassa .01	n.s.

IITR: Registro Internazionale; NAITR: Registro Nordamericano; GITR: Registro Tedesco; SITR: Registro Spagnolo; PROFIT: Registro Italiano; *negli emofilici A gravi. **Nelle caselle sono riportate le p univariate (sopra) e/o multivariate**

the Italian ITI Registry

TIME INTERVAL INH DIAGN. – ITI (mo.)	≤ 1	1-6	6-12	12-24	>24
n	12	16	22	40	48
SUCCESS, n (%)	4 (33)	12 (75)	11 (50)	14 (35)	29 (61)

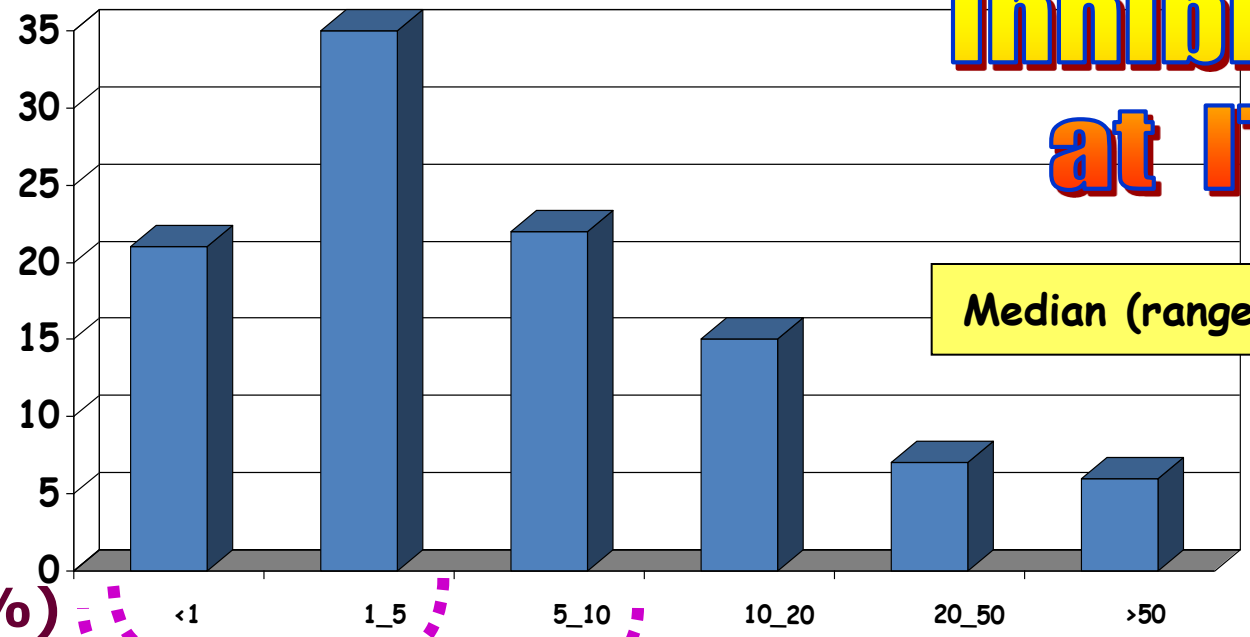
<10 BU at ITI start (% of success)	3/4 (75)	9/12 (75)	9/11 (82)	13/14 (93)	26/29 (89)

No significant impact of time between inh diagnosis and ITI start on success

Trend to greater effect of inh titer at ITI start in delayed ITI

the Italian ITI Registry

Inhibitor titre at ITI start



Median (range): 4.5 BU/ml (0-200)

n=137

59 (54%)

81 (74%)

	success	Non success	P univariate OR (95% C.I.)	P, log. regr. OR (95% C.I.)
Titer at ITI start	2.4 (0-56)	7.3 (0-200)	<0.0001	<0.0001
< 10 BU/ml	49 (87%)	30 (58%)	5.1 (1.7-15.2)	-
< 5 BU/ml	42 (72%)	17 (33%)	6.3 (2.3-14.3)	11.2 (3.2-35.4)

Coppola et al , J Thromb Haemost 2009; Coppola et al, ISTH 2015

The dose issue depends on inhibitor titers

IITR and NAITR, metanalysis n=278
Kroner, Vox Sang 1999

NAITR, influence of FVIII dose and ITI outcome

Dose (U Kg^{-1} day^{-1})	≥200	100–199	50–99	<50	*P*
All haemophilia A subjects					
Success (%)	41	74	72	83	0.03
Months to Success	11	8.5	8	13	*ns*
High responder haemophilia A with pre-ITI <10 BU					
Success (%)	–	84	78	100	*ns*
Months to Success	–	6.4	6.5	18.8	0.007

DiMichele, Haemophilia, 2009

Historical titre (BU)	Pre-ITT titre (BU)	Dose (U kg^{-1} d^{-1})	Successes # (%)
<50	<10	<50	30/36 (83%)
		50–99	33/38 (87%)
		100–199	18/19 (95%)
		≥200	23/24 (96%)
	10–20	<50	2/3 (67%)
		50–199	11/14 (79%)
		≥200	3/4 (75%)
	>20	50–199	3/9 (33%)
		≥200	1/3 (33%)
50–200	<10	<50	8/12 (67%)
		50–99	14/17 (82%)
		≥200	3/4 (75%)
	10–20	50–199	2/6 (33%)
		≥200	3/4 (75%)
	>20	50–199	8/12 (67%)
		≥200	5/7 (71%)
>200	<10	50–199	5/11 (45%)
		≥200	7/7 (100%
	10–20	50–199	1/3 (33%)
		≥200	3/4 (75%)
	>20	50–199	1/23 (4%)
		≥200	12/18 (67%)

International ITI Study - Hay & DiMichele (2002-2009)

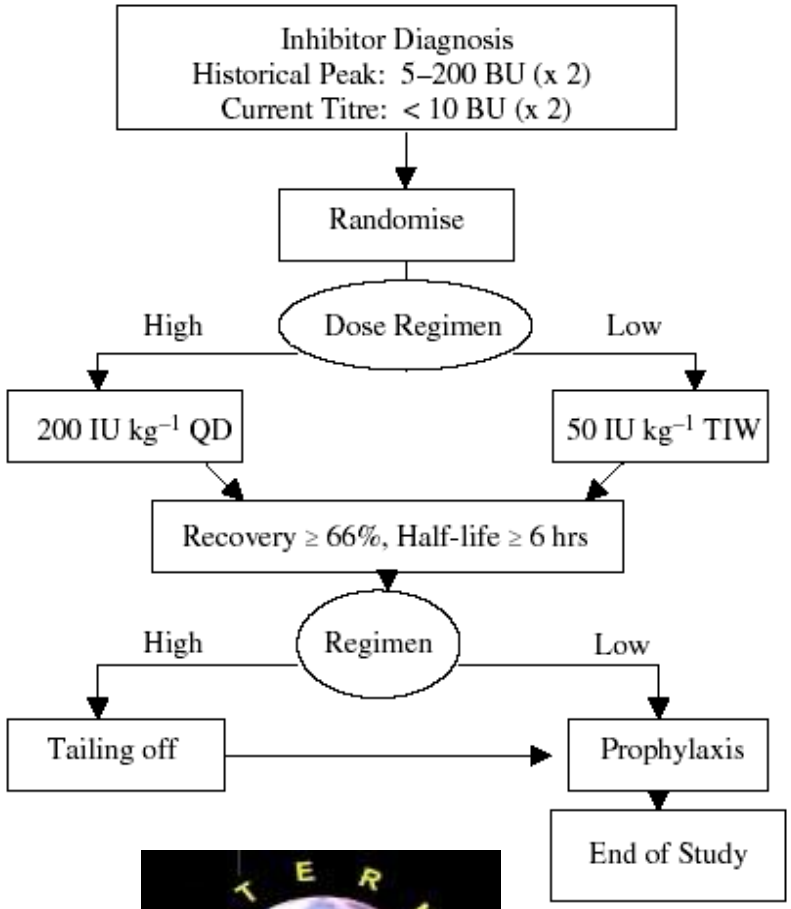
Inclusion Criteria

- ✓ Severe, HR inhibitors
- ✓ age ≤ 8 yrs at ITI start
- ✓ Inhibitor diagnosis ≤ 24 mo. prior to ITI start
- ✓ Inh titer <10 BU at ITI start
- ✓ Historical inh peak ≤ 200 BU

<5 yrs since diagn.

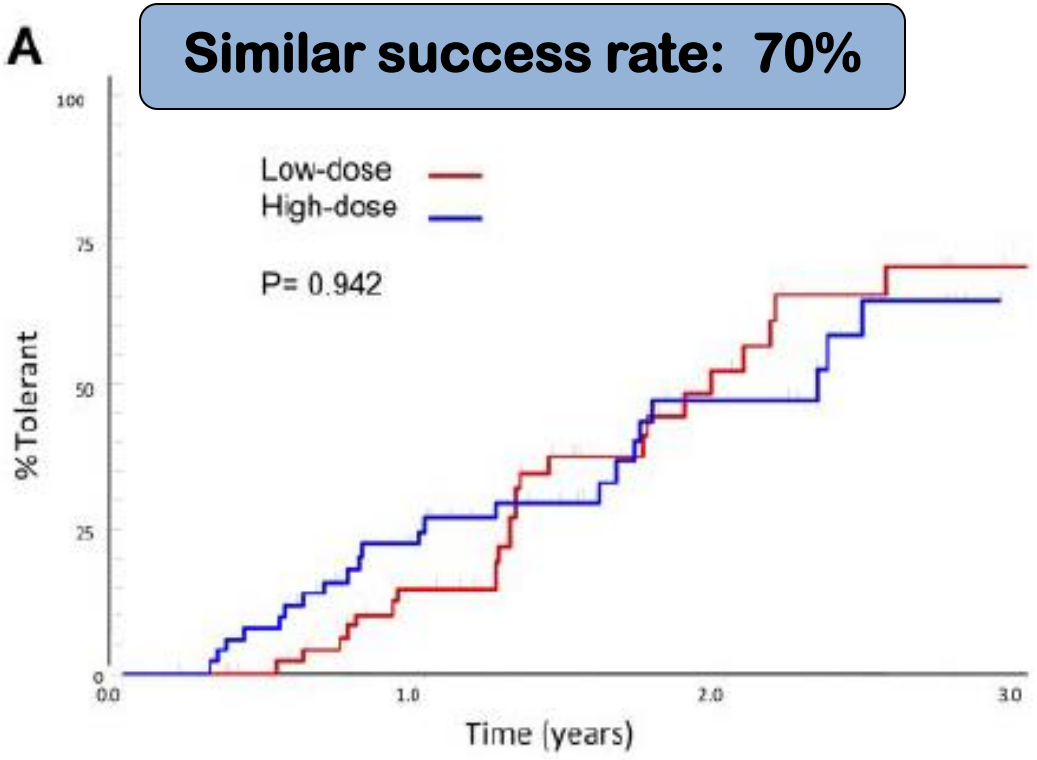
- ✓ First ITI course
- ✓ Stable venous access
- ✓ Informed consent

Good-risk patients, *level IIb*



ITI outcome and predictors of success

Similar success rate: 70%



With the high-dose regimen shorter median time to achieve:
Negative titer (4.6 vs 9.2 mo, p=0.027)
Normal recovery (6.9 vs 13.6 mo, p=0.002)
but not
Tolerance (10.6 vs. 15.5 mo, p=0.116, ns)

Predictors of success

Univariate analysis	
Subject variable	***P***
Ethnicity (white/nonwhite)	.71
Age at randomization (ITI)	.83
Peak historical inhibitor titer	.026
Peak titer on ITI	.002
Peak titer on ITI ≤ 250 versus > 250 BU	.0002
Time to titer of < 10 BU pre-ITI	.40
Starting inhibitor titer	.98
Treatment variable	
Randomized treatment arm	.82
Protocol dose compliance	.35
Product type	.58
Total hospital in-patient days	.088
CVAD in place	.58
CVAD infection	.83
Multivariate analysis	
Peak inhibitor titer on ITI	.002

Hay & Di Michele, Blood, 2012

Bleeding episodes during ITI

N of bleeds	Low-dose	High-dose	HR (95% CI) , p
All ITI	684 (n=58)	282 (n=57)	**2.2** (1.34-3.62) 0.0019
To neg BU	573 (n=58)	241(n=57)	**2.27** (1.29-4.01) 0.0046
To N IVR	47 (n=27)	4 (n=23)	3.4 (0.84-13.8) 0.088
To N T1/2	9 (n=24)	3 (n=22)	5.18 (0.71-38.0) 0.110
prophylaxis	54 (n=24)	32 (n=22)	1.70 (0.80-3.63) 0.170

Mean bleed rate (bleeds/mo)	Low-dose	High-dose	p
To neg BU	0.623	0.282	**0.00024**
To N IVR	0.127	0.087	0.283
To N T1/2	0.150	0.033	0.552
prophylaxis	0.175	0.102	0.112

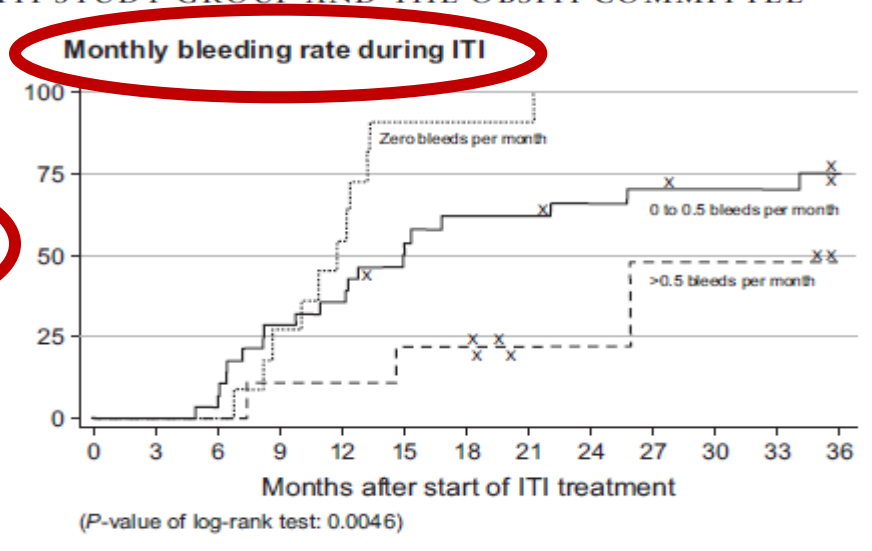
Hay & Di Michele, Blood, 2012

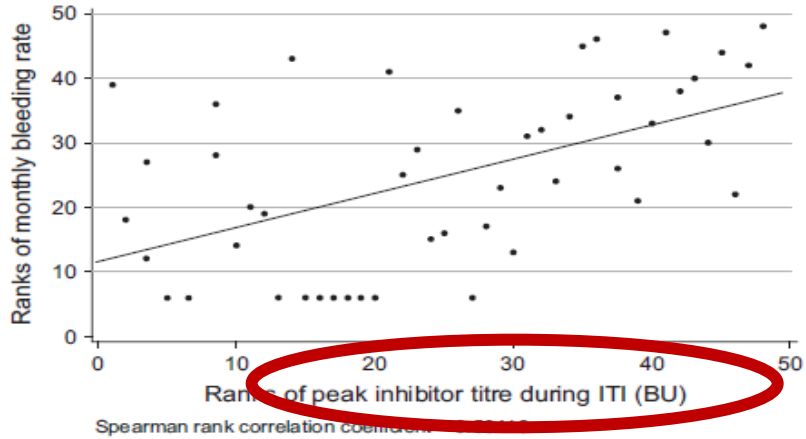
First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/ von Willebrand factor concentrate in an observational immune tolerance induction study

W. KREUZ,* C. ESCURIOLA ETTINGSHAUSEN,* V. VDOVIN,† N. ZOZULYA,‡ O. PLYUSHCH,‡ P. SVIRIN,† T. ANDREEVA,§ E. BUBANSKÁ,¶ M. CAMPOS,** M. BENEDIK-DOLNIČAR,†† V. JIMÉNEZ-YUSTE,‡‡ L. KITANOVSKI,†† A. KLUKOWSKA,§§ A. MOMOT,¶¶ N. OSMULSKAYA,*** M. PRIETO,††† S. Z. ŠALEK,‡‡‡ F. VELASCO,§§§ A. PAVLOVA,¶¶¶ J. OLDENBURG,¶¶¶ S. KNAUB,**** M. JANSEN,†††† L. BELYANSKAYA**** and O. WALTER**** ON BEHALF OF THE OBSITI STUDY GROUP AND THE OBSITI COMMITTEE

	ITI population			
Population	LR (N = 6)	HR (N = 42)	All (N = 48)	HR with ≥1 poor prognosis risk factor (N = 35)
Complete success				
Patients achieving, N (%)	6 (100)	28 (66.7)	34 (70.8)	22 (62.9)
95% CI			55.9, 83.1	44.9, 78.5
Partial success				
Patients achieving, N (%)	0 (0)	3 (7.1)	3 (6.3)	2 (5.7)
95% CI			1.3, 17.2	0.7, 19.6
Partial response				
Patients achieving, N (%)	0 (0)	1 (2.4)	1 (2.1)	1 (2.9)
95% CI			0.1, 11.1	0.07, 14.9
Failure				
Patients achieving, N (%)	0 (0)	10 (23.8)	10 (20.8)	10 (28.6)
95% CI			10.5, 35.0	14.6, 46.3

HR, high responder; ITI, immune tolerance induction; LR, low responder.





Haemophilia (2015)

Which FVIII dose ?

Good-risk patients

No dosing regimen demonstrated superior to another

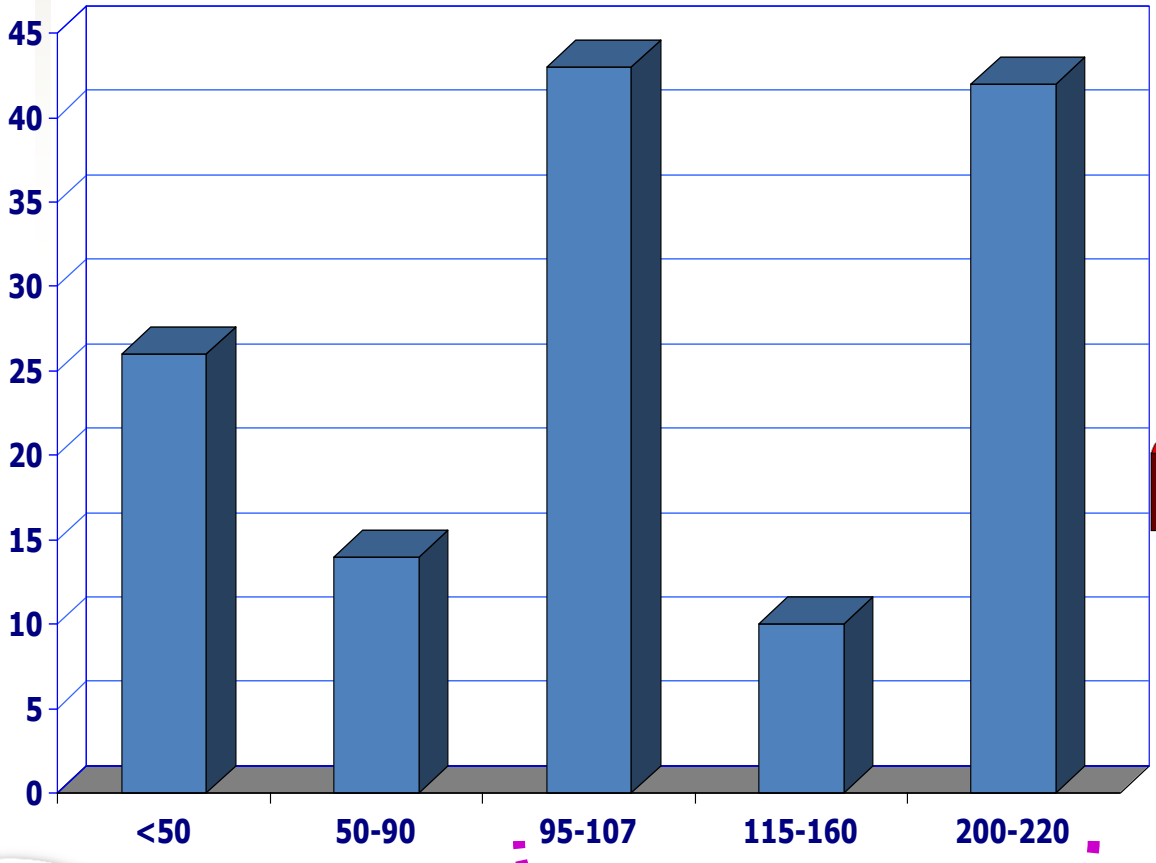
Safety concerns suggest to avoid low-dose regimens* (level Ib)

Efficacy and safety of commonly used, <u>daily</u> intermediate dose regimens (100 IU/Kg vs. high-dose (200 IU/Kg) ?

*particularly in good-risk patients; Hay & DiMichele, Blood 2012

the Italian ITI Registry

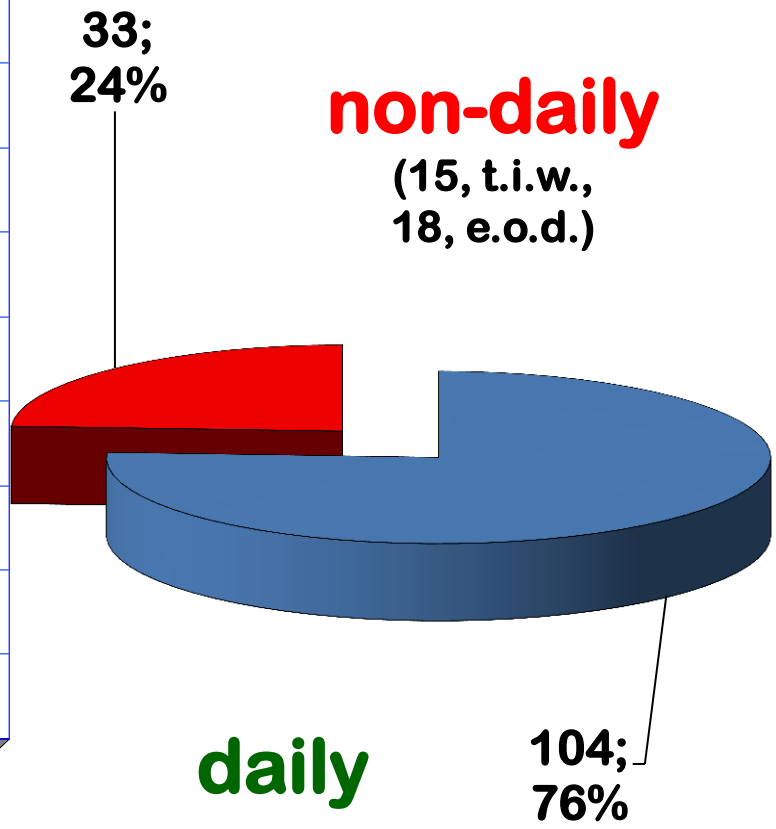
Daily FVIII dose



n=137

97 (70.8%)

Regimens



Which FVIII dose ?

Recommendation

Principles of treatment and update of recommendations for the management of haemophilia and congenital bleeding disorders in Italy

Angiola Rocino[1], Antonio Coppola[2], Massimo Franchini[3], Giancarlo Castaman[4,5], Cristina Santoro[6], Ezio Zanon[7], Elena Santagostino[8], Massimo Morfini[9] on behalf of the Italian Association of Haemophilia Centres (AICE) Working Party (see appendix 1)

intermediate FVIII doses (100 IU/kg/day) have been reported in literature also by Italian clinicians[81,144-146]. Although no direct comparison of such regimens with the classical high-dose regimen is available, similar success rates have been reported, particularly in children with a good-prognosis profile[145,146]. Therefore, ITI can be started with an intermediate dose (100 IU/kg/day) regimen and the dose can be increased in the case of breakthrough bleeding episodes or if high inhibitor peak titres (≥200 BU/mL) are detected during the treatment. This approach, also suggested by the UKHCDO guidelines[78], may contribute to improve cost-effectiveness and cost-utility of ITI and is already frequently used in Italian HTCs[11]. Nevertheless, high-dose regimens should be preferred in patients with a poor prognosis in order to improve the success rate[77,139,141,147].

Which FVIII dose ?

- If the historic peak inhibitor titre is <5 BU/ml, ITI should be started at a dose of 50 iu/kg on alternate days (Grade 2B).
- If the starting inhibitor titre is <10 BU/ml and the historic peak <200 BU/ml ITI should commence with 100 iu/kg/d unless peak is <5 BU/ml (see above) (Grade 2B).
- If the starting inhibitor titre is >10 BU/ml or the historic peak >200 BU/ml ITI should commence with 200 iu/kg/d (Grade 2B).
- If the ITI regimen of 50 iu/kg alternate days or 100 iu/kg/d is complicated by bleeding episodes the dose should be increased in stages up to 200 iu/kg/d to control bleeds (Grade 2B).

What is the appropriate ITI regimen?.

1. For young patients (age <8 years) with adequate venous access and favourable risk factors, FVIII should be given at a dose of 200 IU kg^{-1} day^{-1} (1A) [2].
2. Alternatively, cohort and registry data support the efficacy of daily FVIII 100 IU kg^{-1}. This regimen is favoured in many US HTCs but has not been studied in a randomized clinical trial (1C) [12,13].

Which type of FVIII product ?
the German ITI experience

Frankfurt

	Type of concentrate	Complete ITI (*n*/*n*)	Success rate (%)
1979-93	pd FVIII-VWF	19/21	90
Since 1993	pd FVIII-VWF	2/2	100
	hp FVIII	4/14	29
	Changed to pd FVIII-VWF	8/10	80
Total		14/16	88

Kreuz et al, Haematologica, 2001

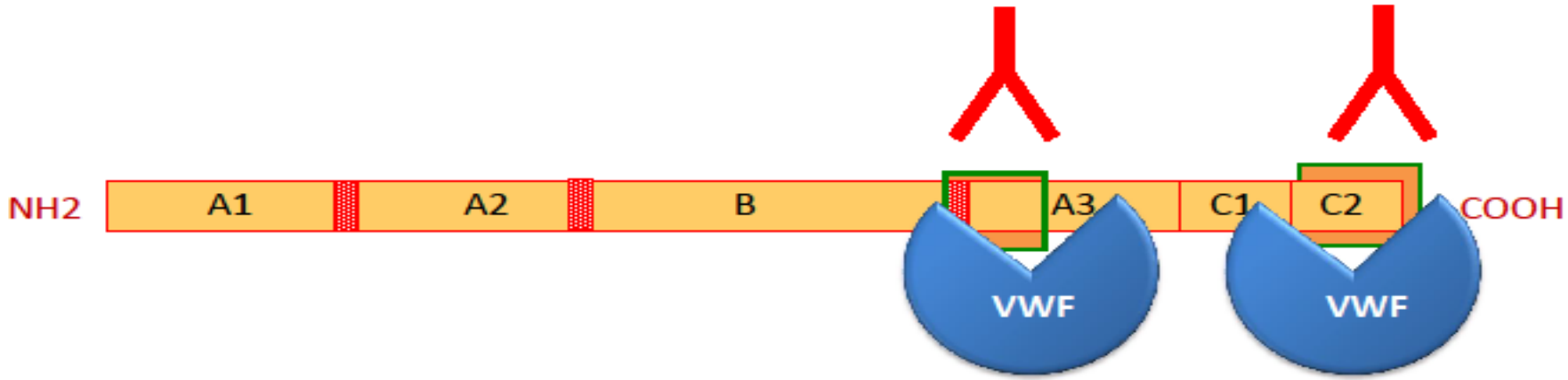
Bonn and Bremen

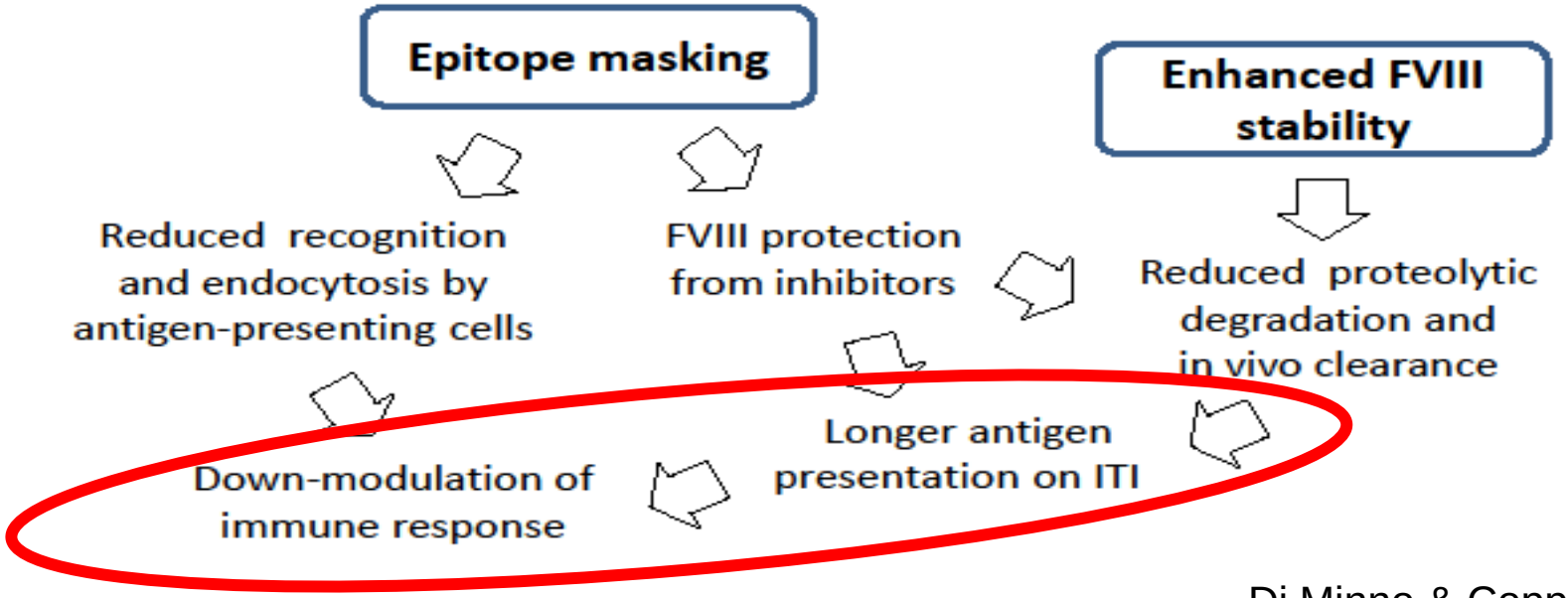
	<1990 *n* = 51	>1990-7/2001 *n* = 42	
	pd FVIII	rFVIII (*n* = 14)	pd FVIII (*n* = 28)
Overall success rate	87%	54%	82%
Success rate (high responder >5 BU)	86%	43%	78%
Success rate (low responder >0.6-5 BU)	93%	72%	91%

Auerswald et al, Haematologica, 2003

All patients treated with the Bonn protocol
Strategy of starting and conducting ITI unchanged
Similar definitions of ITI outcomes

A role for VWF ?





Di Minno & Coppola, 2011

Which type of FVIII concentrate ?

Study	Dose regimen(s)	Type of concentrate (*n**)	Success rate (%)
NAITR, DiMichele and Kroner (2002)†	Various	IP and HP pdFVIII (41)	68
		Mo/rFVIII (123)	71
Mauser-Bunschoten *et al* (1995)	Dutch protocol	Mostly IP pdFVIII (24)	87
Brackmann *et al* (1996)	Bonn protocol	Mostly IP pdFVIII (52)	88
Rothschild *et al* (1998)	Various	rFVIII (8)	25‡
Batlle *et al* (1999)	Various	rFVIII (11)	82§
Smith *et al* (1999)	High-dose	Mo/rFVIII (11)	91
Rocino *et al* (2001)	100 iu/kg/d	Mo/rFVIII (12)	83
Orsini *et al* (2005)	Various	HP pdFVIII (8)	88
Barnes *et al* (2006)	Various	Mostly rFVIII (29)	79§
Rocino *et al* (2006)	Various	rFVIII (26)	73
Gringeri *et al* (2007)	Various	HP pdFVIII (17)	53¶
Kurth *et al* (2008)	100–200 iu/kg/d	IP and HP pdFVIII (25)	32¶
Grenninger *et al* (2008)	Various	HP pdFVIII (11)	45¶
Valentino *et al* (2009)	Various	rFVIII (10)	75

Coppola et al, Br J Haematol, 2010

A COMPLEX, MULTIFACTORIAL ANALYSIS...
TAKING INTO ACCOUNT THE PATIENTS' PROGNOSTIC PROFILE...

Which type of FVIII concentrate ?

- **No definite data support superiority of any FVIII product (level IIb)**
- **Most patients achieve tolerance with same product in use at time of inh detection (level IIb)**

International workshop on immune tolerance induction: consensus recommendations[1]

Haemophilia (2007), **13** (Suppl. 1), 1–22

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

most patients received such products[81,142]. With this uncertainty, no recommendation can be expressed concerning the type of product to be used for ITI in adult patients, who should share the decision with

Rocino et al, Blood Transfus 2014

available information. On the other hand, in patients undergoing ITI early after inhibitor development, usually children on rFVIII concentrates, consistent with expert recommendations[76-78], the same product in use at inhibitor development should be preferred. Alternatively, another recombinant product with similar characteristics could be used.

US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors

L. A. VALENTINO,* C. L. KEMPTON,†¶ R. KRUSE-JARRES,‡ P. MATHEW,§ S. L. MEEKS¶ and U. M. REISS** ON BEHALF OF THE INTERNATIONAL IMMUNE TOLERANCE INDUCTION STUDY INVESTIGATORS

Haemophilia (2015), **21**, 559–567

What FVIII product should be used?.

1. There is insufficient evidence to recommend one product over another (2C) [12,13].
2. When ITI is unsuccessful using a monoclonal or recombinant FVIII product, we recommend considering another attempt at ITI using a pdFVIII/VWF concentrate (2C) [32–36].

2C Weak recommendation, low quality or very low-quality evidence (observational studies or case series)

The benefits of switching to a pdFVIII/VWF concentrate following unsuccessful ITI with a monoclonal or recombinant FVIII product is unknown.

Searching for new predictors: FVIII genotype

Journal of Thrombosis and Haemostasis, 7: 1809–1815 DOI: 10.1111/j.1538-7836.2009.03615.x

ORIGINAL ARTICLE

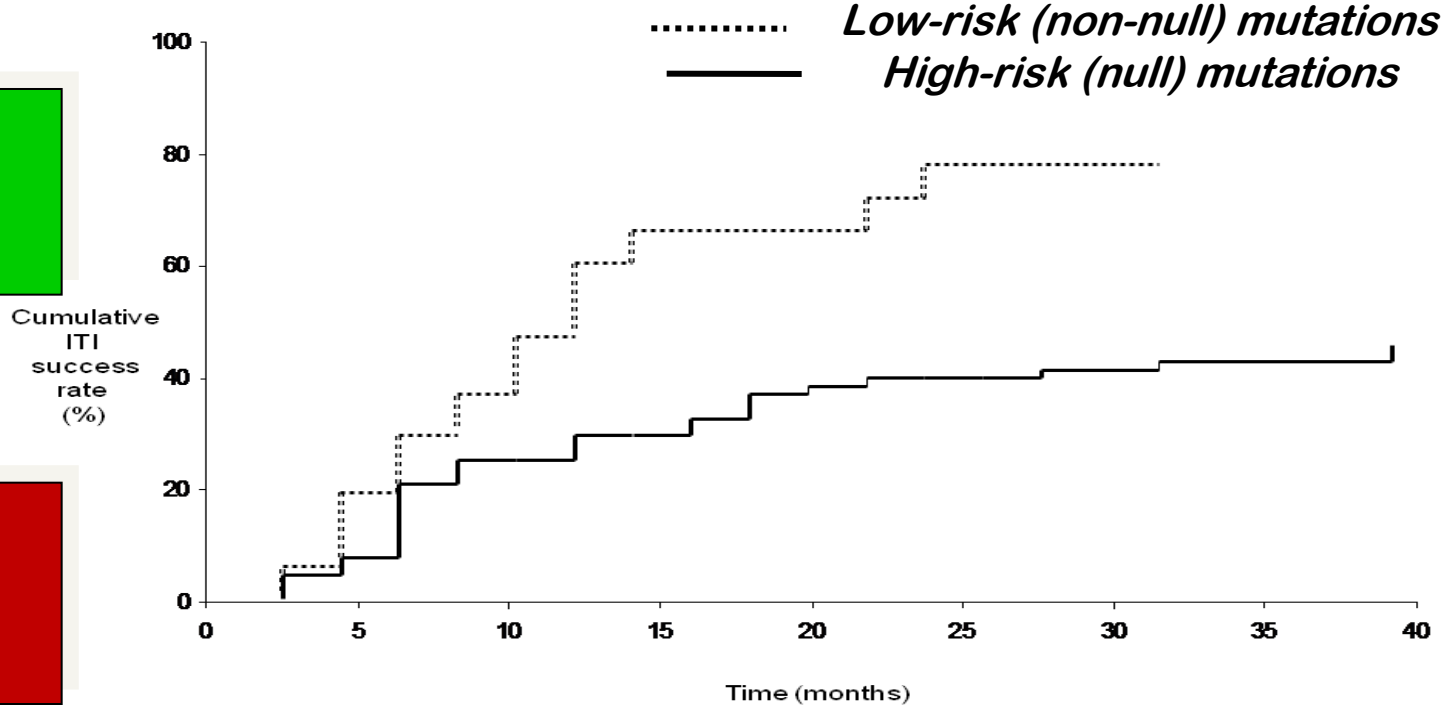
Factor VIII gene (*F8*) mutations as predictors of outcome in immune tolerance induction of hemophilia A patients with high-responding inhibitors

A. COPPOLA,* M. MARGAGLIONE,†‡ E. SANTAGOSTINO,§ A. ROCINO,¶ E. GRANDONE,‡ P. M. MANNUCCI§ and G. DI MINNO* FOR THE AICE PROFIT STUDY GROUP**

*Regional Reference Centre for Coagulation Disorders, Department of Clinical and Experimental Medicine, Federico II University, Naples; †Medical Genetics, University of Foggia, Foggia; ‡Haemostasis and Thrombosis Unit, IRCCS 'Casa Sollievo della Sofferenza', S. Giovanni Rotondo (FG); §A. Bianchi Bonomi Haemophilia and Thrombosis Centre, Department of Medicine and Medical Specialties, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation and University of Milan, Milan; ¶Haemophilia and Thrombosis Centre, S. Giovanni Bosco Hospital, Naples; Italy; and **AICE: the Italian Asso*

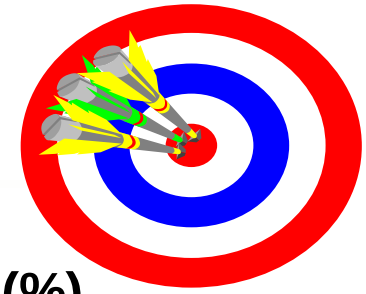
n=86

Time to success non-null vs null mutations



RR (95% CI) 2.4 (1.2-4.9) p=0.01

Data on relapse



	Study	Follow-up	n (%)
COHORT	Mauser-Bunschoten, 1995	8.25 y	1/21 (4.7)
	Kucharski, 1996	8.5 y	0/5 (0)
	Batlle, 1999	nd	1/9 (11.1)
	Unuvar, 2000	nd	1/8 (12.5)
	Rocino, 2006	5.3 y	1/26 (3.8)
	Antun, 2015	1.6 y	20/64 (31.3)^
REGISTRY	NAITR, Di Michele, 2000	1-9 y	9/103 (8.7%)°
	IITR, Mariani, 2001	1-15 y	6/128 (4.7%)*
	PROFIT, Coppola, 2009	4.3 y	2/58 (3.5%)

^at least 1 inh titer ≥0.6 BU/ml **estimated risk of relapse at 15 yrs: 15%*

°only in 1 tolerance defined with normal half-life and in 4 with normal recovery

Definitions of ITI outcomes

Successful tolerance	Negative inhibitor titer, FVIII recovery ≥ 66% of expected, and FVIII recovery ≥ 6 h
Partial response	After 33 mo of ITI, negative inhibitor titer but persistently abnormal recovery or half-life; responding clinically to FVIII replacement without an anamnestic increase in inhibitor titer
Study failure	Failure of the inhibitor to decline by ≥ 20% over any 6-mo period after the first 3 mo of immune tolerance induction (ITI); or failure to achieve tolerance or partial response after 33 mo on ITI; or withdrawal from the study for any reason before tolerance was achieved
Relapse	Inhibitor recurrence during the 12-mo follow-up period on prophylaxis after tolerance was achieved, as evidenced by recurrent positive Bethesda titer or a decline in FVIII recovery or half-life below study limits

2 Int. Conference on Immune Tolerance Therapy, Bonn 1997 (unpublished)

International workshop on immune tolerance induction: consensus recommendations[1]

Haemophilia (2007), **13** (Suppl. 1), 1–22

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

Hay & Di Michele, Blood, 2012

Definition of outcome: evolving concepts

measurement of FVIII half-life in patients with low-titre inhibitors is difficult for most haemophilia centres, that the normal FVIII half-life of an individual patient is unknown and that a FVIII half-life of 6 h is likely to be too short to be a suitable criterion for tolerance. The definition used for restoration of normal pharmacokinetics is, therefore, a post-washout half-life of >7 h or a measureable FVIII trough level at 48 h in an individual receiving standard prophylaxis (20–50 iu/kg).

Collins et al, UKHCDO, Br J Haematol 2012

Frankfurt and Bonn study centres [7]. The three efficacy criteria were: Criterion I – inhibitor titre <0.6 BU; Criterion II – FVIII recovery ≥80% of the predefined reference value of 1.5% IU^{-1} kg^{-1} bw ≤1 h post injection; Criterion III – FVIII half-life ≥7 h.

Complete success required achievement of all three criteria; *partial success* required achievement of two and *partial response* required achievement of one of the three criteria. If no criteria were met within the 36-month observation period, i.e. presence of a persistent inhibitor, this was considered an *ITI failure*. Withdrawal from the study for administrative reasons was considered an *ITI failure*. Relapse monitoring was performed over 12 months using Bethesda assay

Kreuz et al, OBSITI, Haemophilia 2015

Immunomodulation/suppression

Haemophilia (2006), 12, 363–371 DOI: 10.1111/j.1365-2516.2006.01296.x

Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors

J. ASTERMARK,* M. MORADO,† A. ROCINO,‡ H. M. VAN DEN BERG§, M. VON DEPKA¶, A. GRINGERI,** L. MANTOVANI,†† R. P. GARRIDO,‡‡ M. SCHIAVONI,§§ A. VILLAR,† and J. WINDYGA¶¶ ON BEHALF OF THE EHTSB[1]

- Immunoabsorption might be considered in patients with high inh titer at ITI start (grade B, level III)
- Immunosuppression should be considered in association with ITI only in patients with high-titer, long-standing inh, unresponsive to other treatments (potential side effects)

- **No role as first-line component of ITI for immunoabsorption (level IIb).**
- **Consider adding rituximab or other immune-modulating agent to the current regimen in the case of incomplete or lack of response**

International workshop on immune tolerance induction: consensus recommendations[1]

Haemophilia (2007), **13** (Suppl. 1), 1–22

D. M. DIMICHELE,* W. K. HOOTS,† S. W. PIPE,‡ G. E. RIVARD§ and E. SANTAGOSTINO¶

- **Rituximab: metanalysis, Franchini et al, 2009**

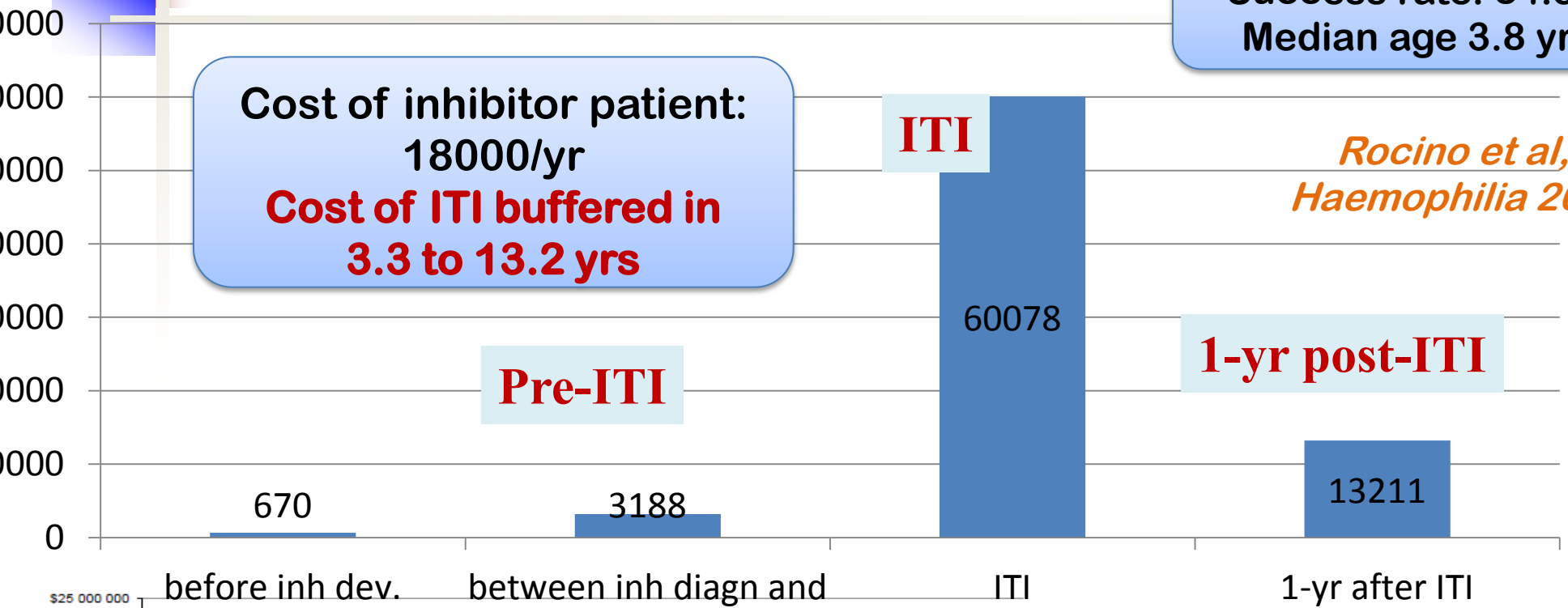
Cost-utility of inhibitor treatment

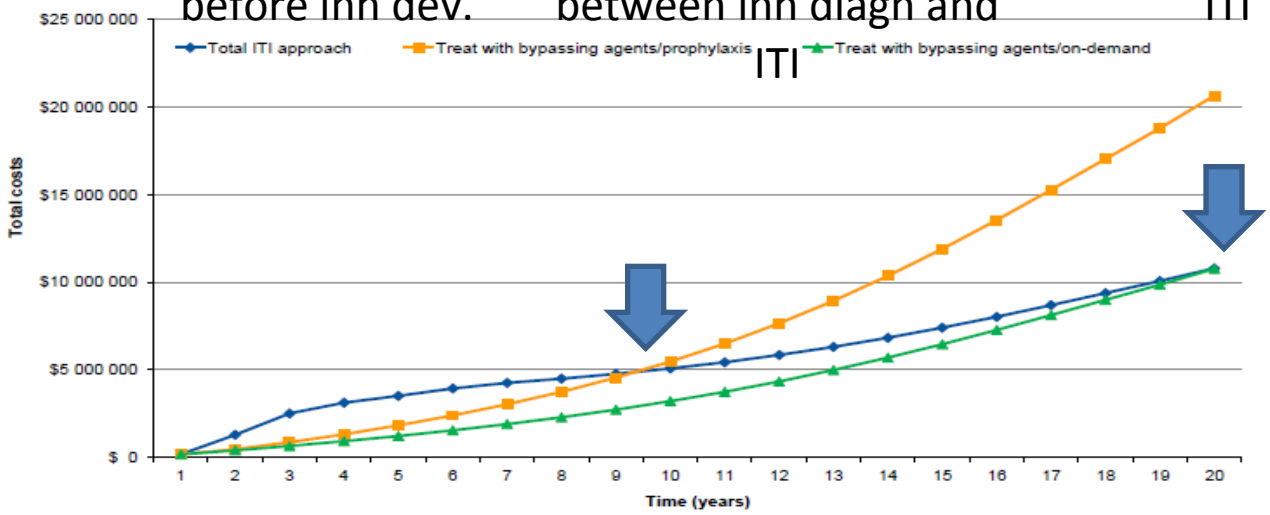
Cost of treatment (€/patient-mo)

ITER Study n=71
Success rate: 84.5%
Median age 3.8 yrs

Cost of inhibitor patient: 18000/yr
Cost of ITI buffered in 3.3 to 13.2 yrs

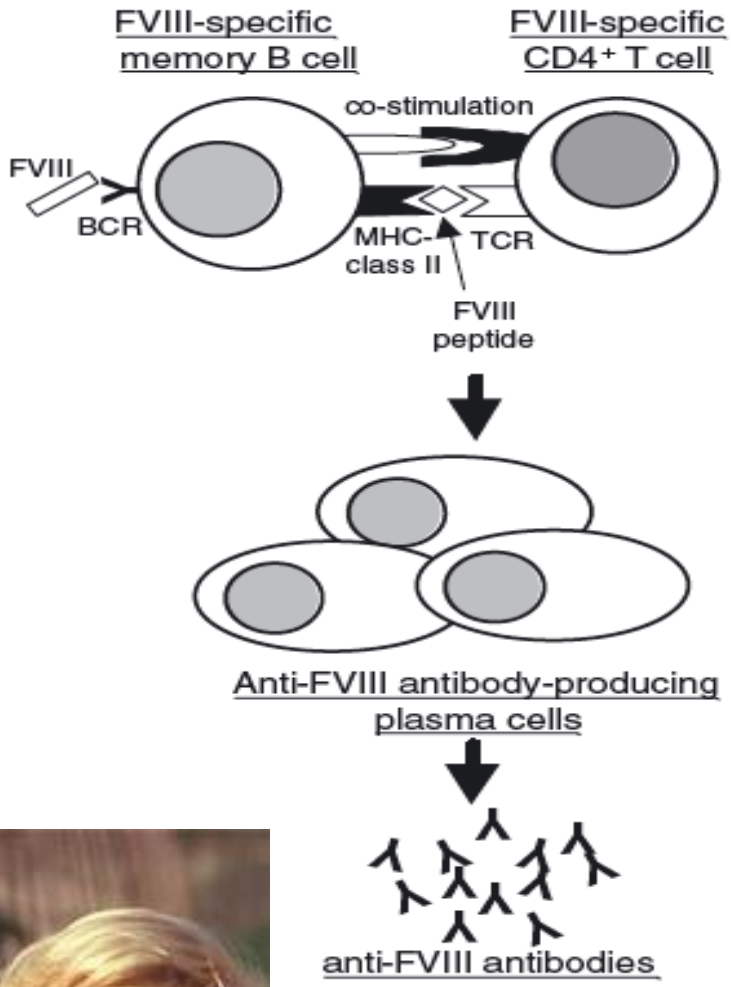
Rocino et al, Haemophilia 2015



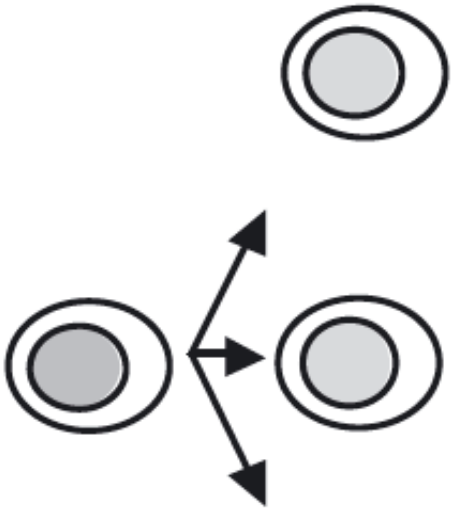


Modello decisionale
ITI: **-77% bleeding** vs. BPA OD
4.3 yrs higher life expectancy
4.3 and 9.9 QALY vs. BPA prophylaxis and OD

Earnshaw et al, Haemophilia 2015



Grazie



Natural Treg
Cells originate from naive precursors in the thymus or periphery. May secrete IL-10 and/or TGF-ß.

IL-10+ Treg/Tr1
Cells induced by repetitive antigen encounter and suppress inflammation through secretion of IL-10.

Th3 cells
Cells induced at mucosal surfaces and suppress inflammation through secretion of TGF-ß

Children with inhibitors

Pros

- Recent-onset inhibitor
- No (or minimal) joint damage
- ITI: optimal clinical target and cost-utility ratio

Cons

- High actual inh titer → wait
- Frequent 'danger signals'
- Venous access, education, adherence.

Adults with inhibitors

Pros

- Low-titer inhibitor
- Usually no venous access problems

- Established, often severe joint damage
- Risk of severe (even fatal) bleeding

ITI: assessment of individual cost-utilty ratio (bleeding tendency, co-morbidities, quality of life, need for orthopedic surgery)

Cons

- Long-standing inhibitors
- Psychological resistance and perceived poor prognosis
- Higher costs

DOI: 10.1111/j.1365-2516.2010.02237.x

Brackmann and Gormsen (*Lancet* 1977; ii: 933): Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder

- 1.5-yr child; severe bleeding in the right shoulder, arm and chest; inh titer >500 BU/ml
- Treatment with high-dose FVIII (100 IU/Kg every 12 hours) and prothrombin complex concentrate (aPCC not available at that time in Germany).
- Control of bleeding. Three weeks later inh 40 BU/ml.
- Treatment (aPCC 50 IU/Kg bid) in other patients. Despite initial inhibitor boosting in some, decrease of inhibitor titer was recorded in all patients and continuation of treatment resulted in inhibitor eradication.

> Thus in 2010, we may be reverting to the regimen pioneered by Brackmann in 1977. This early publication is a great tribute to the clinical observation together with the brave pioneering spirit of Hans Brackmann.

The need for large, modern prospective studies

Observational Immune Tolerance Induction research program

International open-label, uncontrolled, non-interventional, multi-centre observational program conducted by the HZRM, Frankfurt-Mörfelden, Germany

26 countries

26 centers

both retrospective-prospective and established in 2005

PROgnostic Factors in Immune Tolerance

the Italian ITI Registry

Do inhibitors clear spontaneously ?

- Retrospective reports of spontaneous clearance
  - 62/101 (61%) LR and 8/79 HR (10%) inhibitors within 6 months *Tagariello et al, J Hematol Oncol 2013*
  - 5/9 (56%) LR and 1/29 HR (3%) inhibitors *Caram et al Thromb Haemost 2011*

- Prospective data in rFVIII trials: transient inhibitors

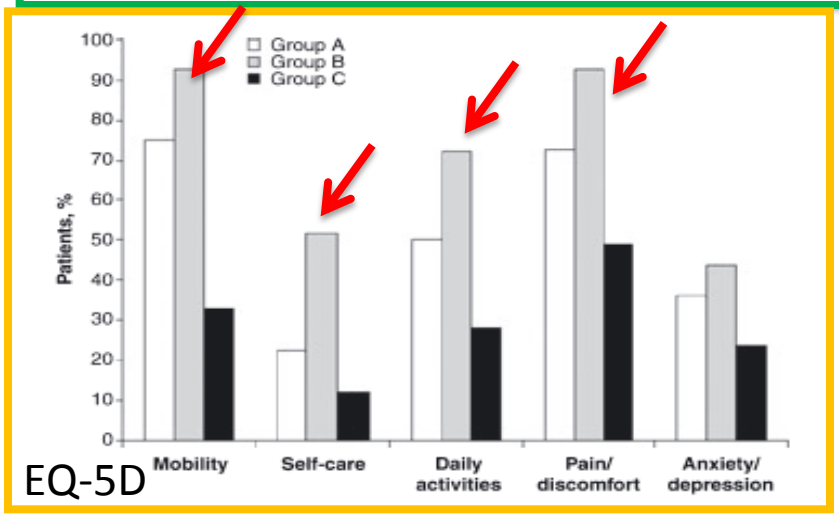
Study	HR inhibitors (%)	LR inhibitors (%)
Rotschild 2000, Recombinate	0/7 (0)	5/15 (33)
Lusher 2004, Kogenate	1/6 (9)	6/8 (75)
Lusher 2003, Refacto	1/12 (8)	8/20 (40)
Kreuz 2005, Kogenate Bayer	0/5 (0)	2/4 (50)
Auerswald 2012, Advate*	n.a.	1/4 (25)
All	**2/30 (7)**	**22/51 (43)**

*for those not undergone ITI

Il paziente con inibitore:

compromissione stato articolare e qualità di vita

	Group A (n = 38)	Group B (n = 41)	Group C (n = 49)	Group A vs. C	
				95% CI	P
Pain evaluation†					
Major joints	3.13 (±2.76)	4.64 (±4.11)	1.90 (±2.19)	0.45–1.77	*ns*
All joints	3.89 (±3.26)	5.82 (±5.29)	2.27 (±2.67)	0.76–2.68	<0.05
Clinical examination*					
Major joints	14.6 (±12.2)	20.2 (±9.48)	5.27 (±6.20)	4.49–12.18	<0.05
All joints	15.4 (±13.6)	23.2 (±11.6)	5.46 (±7.11)	8.40–14.30	<0.05
Radiological evaluation†					
Major joints	22.9 (±14.3)	31.8 (±16.2)	8.00 (±10.2)	8.25–24.10	<0.05
All joints	27.8 (±19.6)	35.8 (±26.4)	19.3 (±12.4)	–	*ns*



EQ-5D

Gruppo A: pazienti inibitore HR 14-35 anni

Gruppo B: pazienti inibitore HR 36-65 anni

Gruppo C: pazienti senza inibitore

Morfini et al, ESOS, Haemophilia 2007

the Italian ITI Registry

AGE AT ITI START (yr.)	≤ 8	8-14	14-25	>25
n	82	14	16	25
SUCCESS, n (%)	43 (52)	7 (50)	7 (44)	13 (52)

<10 BU at ITI start (% of success)	35/43 (81)	6/7 (86)	6/7 (82)	11/13 (85)

No significant impact of age at ITI start on success
The large majority of successful ITI started with low inh titers