Inhibitors in children and in adults
Why they are different and what do they have common?

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Introduction

Inhibitors in haemophilia

- The development of inhibitors is one of the most serious complications of the treatment in patients with haemophilia
  - Brackmann et al., Eur J Haematol Suppl, 1998
- They develop in 4-20% of HA patients with the percentage rising up to 52% in certain populations
  - Manno, Haemophilia, 1999
- Less frequent in HB: 1,5-3% only –"orphan disease"
  - Lack of useful evidence on treatment outcome predictors, risk factors, diagnosis and treatment
  - Frequent allergic reactions, nephrotic syndrome
    - Di Michele, Br J hematol, 2007

How to treat inhibitor patients ?

- **ITI is the first-line treatment in children**
  - Commenced during 1st year after inhibitor development
  - In adults ITI applied remarkably less often
    - Auerswald et al., Haemophilia 2004
- **Bleeding prophylaxis prior to, during (and perhaps also outside) ITI**
  - rFVIIa
  - aPCC
- Long-time/life-long on demand (OD) treatment with:
  - rFVIIa
  - aPCC
  - Porcine FVIII (seldom in these days)
  - High dose of FVIII
    - Auerswald et al., Haemophilia 2004
    - Brackmann et al., Blood Coagul Fibrinolysis, 2000
    - Morfini et al., Haemophilia 2007

Inhibitors in children

ITI – first line treatment

ITI – three main regimens (HA)

- Malmo
  - Cost effective
  - Relatively quick
  - Uses immune adsorption and perhaps immune suppression
  - Not the “threatment of choice” in these days
- Bonn
  - Relatively expensive
  - May take up to 3 years
  - Recommended especially for high titres inhibitors
- Low(er) dose regimen
  - Relatively cheap
  - Effective enough
  - May take long time, but seldom with complications
  - **CVL less imperative**
- In average
  - Effective in up to 80% of cases
    - Di Michelle et al, Thromb Haemost, 2002; Smith, Pathophysiol Haemost Thromb, 2002
  - Bleedings treated with by-passing agents (nowadays rFVIIa, aPCC)

ICP recommendations – When to start?

The International Consensus Panel (ICP)
Donna DiMichele, Chair

Charles Hay	Keith Hoots
Thiery lambert	Johannes Oldenburg
David Lillicrap	Pia Petrini
Steve Pipe	Mike Recht
Mark Reding	Georges Rivard
Chantal Rothschild	Elena Santagostino

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

International ITI Workshops – (Jun&Sep, 2006)

Preferred start of ITI if titre < 10 BU

When to start?

Wait until Inh titre < 10BU

- Pre ITI treatment of inh patients with by-passing agents
- Recommended : rFVIIa (90-270µg/kg/d)

Start ITI regardless of inh titre (<10 BU) if

- Waiting period > 1-2 years
- Severe/life-threatening bleeds occurs

NB: Both (aPCC and rFVIIa) recommended if bleeding occurs

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

Use of rFVIIa to optimise conditions for ITI

"The exclusive use of rFVIIa in acute bleeding episodes prior to commencing ITI is an effective method of decreasing inhibitor titre, thereby optimizing conditions for ITI"

Brackmann H, et al., Bood Coagul Fibrinolysis 2000; 11(Suppl 1):S39-44

I - ITI study

- Compared two ITI strategies (in HA)
  - HD (200IU/kg daily) vs. LD (50IU/kg thrice/week)
  - In good risk, severe, high titer HA inhibitor pts.
- No difference in success rate
  - (24/58 LD vs. 22/57 HD, p=0,909)
  - Shorter time to achieve neg. titer (p=0,027), normal recovery (p=0,002) and tolerance (p=0,116 NS) in HD group
- Peak inhibitor titers correlated inversely with success rate
  - Historical peak (p=0,026), on-ITI peak (0,002)
  - ONLY on-ITI peak predicted outcome (p=0,002)
- LD subjects bled more often (p=0,0019, OR 2,2)

» Ch Hay and D Di Michelle, Blood 2011

Inhibitors in Haemophilia B

- Rare&less understood disease, mostly in severe HB patients
- High morbidity, difficult to treat
- Severe allergic reactions
  - Difficult to treat with aPCC (contains FIX)
    - rFVIIa only available for bleeding treatment
      - Effective also for prophylaxis
        - » Warrier et al. Blood Coag Fibrinol 1998, Vox Sang 1999
        - » Hay et al. BJH 2006
  - Nephrotic syndrome might complicate the disease
- ITI in HB to be considered **carefully**

ITI in Haemophilia B

- Poor overall success rate (25%)
- High risk of complication
  - Allergy, anaphylaxis, nephrotic syndrome
- Need for immune suppression to decrease risk of complications and increase success rate
  - E.g. Mycofenolate mofetil (MMF) + dexamethasone (DEXA) + IvIG
    - » Wermes et al. Blood 2000
    - » Klarmann et al. Haemophilia 2008
- Low iFIX titre before the ITI start and some way of bleeding prophylaxis is favourable

Question 1

- What will you prefer for the treatment of 2 yrs old severe HA boy with HR inhibitors?
  - A) Increase the dose of FVIII
  - B) ITI protocol
  - C) By-pass medication on demand
  - D) Prophylaxis with By-pass, but no ITI

Question 2

- Which ITI regimen will you choose for 3yrs old HA boy with peak inhibitor titre 450 BU and pre-ITI titer 15 BU?
  - A) I will not go for ITI as this a poor risk patient
    - Will continue on By-pass Tx/Prophy
  - B) I will choose LD regimen
  - C) I will go for HD regimen

Question 3

- Do you have experience with bleeding prophylaxis with By-pass medications?
  - Either within or without ITI
- A) Yes
- B) No

Inhibitors in adults

Registries – results and success prediction

Registry	N	Dose of FVIII IU/kg/D	success (%)	Time to remision (months)	Prediction of success (P < 0,05)					
					Age at ITI start	Inhibitor titre			dose	FVIII mutation
						pre ITI	hist. peak	on ITI		
IITR	314	<50 - ≥200	51	10.5 Median	+	+	+		+	
NAITR	164 128 HR	50 – 200	63 HR	16.3 Mean		+	+	+	+	
GITR	126 104 HR	≥ 200	76 HR	7.6-15.5 Mean			+			
Spain	38	100 - 200	63 HR	9.85 Median		+	+		+	
PROFIT	103 86 HR	median 100	53 HR	8 Median		+		+		+
										47% 81%

**Franchini M, JTH 2011: 10.1007/s11239-011-6243-3*

Is ITI accessible for all patients with inhibitor?

- In 1990s – NAITR:
  - 36% (188/518) received ITI
    - » *Di Michele. Thromb Haemost 2002; 87: 52-7*
- After 2000 – Italian ITI Registry:
  - 54% received ITI
    - 88% (65/74) < 14 years
    - 26% (23/88) > 14 years
      - » *Coppola A. Haemophilia 2012; 18 (Suppl. 3): 88*

Prognostic factors of ITI success: Age and time from inhibitor detection to ITI

- **age:**
  - < 5 years *Hay, Pathophysiol Haemost Thromb 2002: (Suppl 1) 19-21
  - < 20 years: success:
    - < 5 years: 70% (38/54)
    - 5 – 10 years 73% (33/45)
    - 11 – 20 years 78% (36/46)
    - > 20 years 40% (19/47)

    *Mariani G, Semin in Thromb Hemost 2003: 69-75
- **Interval between dg of iFVIII and start of ITI < 5 years**
  - IITR (1997) success > 70% *Mariani G,Haematologica 2001: 1186-93
  - + iFVIII pre-ITI < 10 BU / ml
  - + dose of FVIII >100 IU / kg / D
    - 65% tolerance till 1 year
  - Without these three criteria:
    - 65% success rate was not achieved for at last 31. months

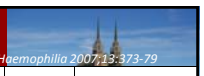
    *Ananyeva, Blood Coagul and Fibrinolys 2004: 109-124

ITI results in adult patients from the Spanish registry

Patient	Inhibitor titre (BU/ml)		Time from inhibitor dg. to ITI (months)	Age at start of ITI (years)	FVIII (1xFIX) IU/kg/ day	Time to inhibitor elimination (months)	Inhibitor after ITI (BU/ml)
	max	pre-ITI					
1	16	16	1	22	100	2	0
2	41	-	-	21	50	3	0
3	22	8	60	25	50	4	0
4	76	17	192	32	200	4	0
5	121	7	60	57	50	7	0
6	36	2	108	35	200	8	0
7	192	22	228	39	Malmö	4	179
median	**41**	**12**	**84**	**32**	**75**	**4**	**CR 6/7 (86%)**
All: 1-38 median	**67**	**11**	**25**	**7**	**140**	**10**	**CR 26/38 (68%)**

*Haya S. Haemophilia 2001;7:154-159

ITI results in adult patients with VWF/FVIII: ≥ 1 poor prog f. (age >6 years, >1 year from inhibitor development, >200 BU hist. peak, > 10 BU pre-ITI, previously failed ITI)



*Gringeri A. Haemophilia 2007;13:373-79

Patient	Inhib. titre (BU/ml)		Time from inhibitor dg. to ITI (years)	Age at ITI start (years)	FVIII IU/kg/day	ITI duration (months)	Inhibitor after ITI (BU/ml)
	max	preITI					
1	18	5	6	45	3x weekly 50	11	< 0,5
2	50	6	18	33	3x weekly 50	21	1,22 - PR
3	30	5	13	23	3x weekly 50	4	< 0,5
4	128	6	22	23	100	33	2,2 - PR
5	737	4	18	53	3x weekly 50	25	< 0,5
6	110	5	33	54	100	12	< 0,5
7	93	2	14	24	3x weekly 50	9	< 0,5
8	45	5	1	36	3x weekly 50	12	70 - Failure
9	54	14	10	31	100	12	< 0,5
Median adults	**54**	**5**	**14**	**33**	**21.5**	**12**	**CR 6/9 (67%) PR 2/9 (22%)**
Median children	**54**	**6.5**	**6**	**13**	**100**	**26.5**	**CR 3/8 (37.5%) PR 5/8 (62.5%)**
All:1-17	**54**	**5**	**8**	**23**	**25**	**23**	**CR 9/17 (53%) PR 7/17 (41%)**

ITI results in adult patients
(assotiation of clinical outcome with inhibitor epitope profile)

Patient	Inhibitor titre (BU/ml)		Time from inhibitor dg. to ITI (months)	Age at start of ITI (years)	FVIII IU/kg/ week	ITI duration (months)	Inhibitor after ITI (BU/ml)
	max.	pre-ITI					
1	150	8	210	20	300	9	< 0,6
2	89	4	4	37	150	28,5	< 0,6
3	288	1,4	207,5	22	300	16,2	< 0,6
median	**150**	**4**	**207,5**	**22**	**300**	**16,2**	**CR 3/3 (100%)**
1-7 median	**89**	**5**	**16**	**8,2**	**700**	**22,75**	**CR 5/7 (71%) PR 2/7 (29%)**

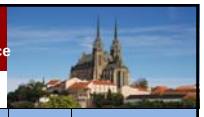
**Gringeri A. Haemophilia 2008;14:295-302*

ITI results in adult patients - Hungary

No	age (years) mean	Inhibitor titre (BU/ml)		FVIII dose (IU/kg/day) mean	Time to inhibitor elimination (months)	success
		maxim. mean	pre-ITI mean			
7	31,8	139,8	22,6	150	5,4	5/7 (71%)

**Nemes L.4th Inhibitor Workshop for Opinion Leaders in Hemophilia, Dubrovnik 2006*

Cost of care anylysis for ITI in adult patients: comparison with rFVIIa ObsITI study: Russian experience



	No.of bleeds per year median	Dose of rFVIIa for one bleeding median	ITI dose of FVIII	CR time to CR median	Cost 10 years preITI rFVIIa (mil. €)	Cost 10 years: ITI + profyl (mil. €)	Saved during 10 years (mil. €)	Break-even point ITI + FVIII prophyl. vers. 10 years on demand rFVIIa
LR n = 3	26	4 x 96 µg/kg	50-100 U/kg daily to alter d.	**3 / 3 9 months**	6.4	2.2	4.2	**1,2 year**
HR n = 7	22	4x 104 µg/kg	100-150 U/kg á 12 h	**5 / 7 10 months**	3.8	2.8	1	**6,8 years**

** Zozulya N. WFH Congress 2010*

ITI results in adult patients with inhibitor: – rate of success

- IITR 2001:
  - **19/47 (40%)**
- Spanish registry + Gringeri 2007:
  - 6/7 + 6/9 = **12/16 (75%)**
- \+ Gringeri 2008 + ObsITI:
  - +3/3 + 5/7 = **20/26 (77%)**
- \+ Nemes 2006:
  - + 5/7 = **25/33 (76%)**
- In total: IITR + Spanish registry + Gringeri 2x + Nemes:
  - **44/80 (55%)**

Why immune tolerance induction?

Factor substitution is better than bypassing activities:

- Higher efficiency of haemostatic treatment:
  - Haemostatic effect with FVIII/FIX is kept for longer time than using by-passing activities
- Simple monitoring
- **Lower cost of treatment:**
  - Treatment of bleeding episodes 10x
  - Turgery 20x
  - Prophylaxis

Treatment of bleeding episodes in patients with inhibitor – registries

(rFVIIa 1 µg = 0.67 €)

Adult patinet, 75 kg, 300 µg/kg ~ 15 000 €

registry	No. of bleeds	rFVIIa per blleding episode			
		haemarthroses		all bleeding episodes	
				children	adults
HTRS **Yung GA, Kessler CM, ISTH Congress 2009*	2041	median 480 µg/kg		median 480 µg/kg	median 270 µg/kg
		Children	adults		
DOSE **Gruppo RA, WFH Congress 2010*	158	median 1245 µg/kg	median 442 µg/kg	median 900 µg/kg	median 462 µg/kg
ONE **Santagostino E, Symp. NovoNordisk 2011*	494			median 192 – 270 µg/kg	
HemoRec **Salaj P Haemophilia 2009*	128				median 193 µg/kg

Surgery (major/orthopaedic) in patient with inhibitor (rFVIIa 1 µg = 0.67 €)

	Initial bolus	Day 1 - 2	Day 3 – 4	Day 5 - 7	Day 8 till 10 – 14	Day 15 - 21	In total
rFVIIa	90 – 180 µg/kg	90 µg/kg á 2 h	90 µg/kg á 3 h	90 µg/kg á 4 h	90 µg/kg á 6 h	90 µg/kg 1 daily	
In total	90 – 180 µg/kg	2 160 µg/kg	2 160 µg/kg	1 620 µg/kg	1 080 µg/kg to 2 520 µg/kg	630 µg/kg	**7 740 µg/kg to 9 120 µg/kg**

Adult patient, 75 kg ~ 400 000 - 450 000 €

** Rodriguez-Merchan EC. Haemophilia 2004; 10 (Suppl. 2): 50-52*
** Giangrande PLF. Haemophilia 2009; 15: 501-8*

Immune tolerance induction (cost)

- adult patient 75 kg
- 1 IU pdFVIII = 0.63 €
- 1 IU rFVIII = 0.79 €

(price in Germany 2004)

**Auerswald, Haemophilia 2004*

Consumption per 1 year	FVIII (IU)	€
low responder 50 IU / kg / D	1 368 750	**rFVIII: 1 081 312 pdFVIII: 862 312**
high responder 200 IU / kg / D	5 475 000	**rFVIII: 4 325 250 pdFVIII: 3 449 250**

Cost-effectiveness of ITI, 4 patients, 75 kg, success 75%:

(max. titr <200 BU, pre-ITI < 10-20 BU)
(Czech Republic: FVIII 1 IU = 0.4 €, rFVIIa 1 µg = 0.67 €)

Daily dose of FVIII	FVIII dose per year	FVIII dose per year per 75 kg	Cost of FVIII per year	Cost of FVIII per 18 months of ITI
100 IU/kg	36 500 IU/kg	2 737 500 IU	1 095 000 €	1 642 500 €
150 IU/kg	54 750 IU/kg	4 106 250 IU	1 642 500 €	2 463 750 €
200 IU/kg	73 000 IU/kg	5 475 000 IU	2 190 000 €	3 285 000 €
300 IU/kg	109 500 IU/kg	8 212 500 IU	3 285 000 €	4 927 500 €

rFVIIa 300 µg/kg per bleeding episode:

Bleeds / year	rFVIIa per year	rFVIIa/year per 75 kg	Cost of rFVIIa per year	Cost of rFVIIa per 10 years	4 patients, after ITI saved annually
5	1 500 µg/kg	112 500 µg	75 375 €	753 750 €	**15 524** €
10	3 000 µg/kg	225 000 µg	150 750 €	1 507 500 €	**241 650** €
20	6 000 µg/kg	450 000 µg	301 500 €	3 015 000 €	**693 900** €
40	12 000 µg/kg	900 000 µg	603 000 €	6 030 000 €	**1 598 400 000** €

After ITI prophylaxis FVIII 45 IU/kg/week:

FVIII per year	FVIII / year/ 75 kg	Cost of FVIII per year	Cost of FVIII per 10 years
2 340 IU/kg	175 500 IU	70 200 €	702 200 €

Question 4

- What will you prefer for the treatment of 30 yrs old severe HA man with HR inhibitors persistent from his childhood?
  - A) ITI protocol
  - B) ITI protocol according to bleeding frequency
  - C) By-pass medication on demand
  - D) Prophylaxis with By-pass, but no ITI

Question 5

- Which ITI regimen will you choose for this 30yrs old HA man with peak inhibitor titer 450 BU and current inhibitor titre 15 BU?
  - A) I will not go for ITI as this a poor risk patient
    - Will continue on By-pass
  - B) I will choose LD regimen
  - C) I will go for HD regimen
  - D) I will postpone the initiation of ITI until the inhibitor titre drops down to < 10 BU
    - After that I will go for HD ITI

Question 6

- What will you prefer for the treatment of 40 yrs old severe HA man with new diagnosed LR inhibitors?
  - A) ITI protocol
  - B) high dose of FVIII concentrate
  - C) By-pass medication on demand
  - D) ITI protocol only if:
    - bleeding cannot be treated with FVIII

Question 7

- Which ITI regimen will you choose for this 40yrs old HA man with LR inhibitor but unsuccessful replacement therapy with FVIII?
  - A) I will choose LD regimen
  - B) I will go for HD regimen
  - C) I will go for Malmö protocol
  - D) I will use immune suppression only

Thank you for your kind attention!

Rime (white frost) on the fence

Pasqueflower (Pulsatilla grandis) 10 minutes´ walk from our CCC

On demand or prophylaxis with bypassing agents → **ITI** → **Low dose prophylaxis or on demand treatment with FVIII concentrate**