Bleeding prevention and treatment prior to, during and after ITI

Jan Blatny, MD, PhD

Dept. of Paediatric Haematology
Centre for Thrombosis and Haemostasis
Children's University Hospital Brno,
Czech republic

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
- **Prophylaxis prior to, during** (and perhaps also outside) **ITI**
  - aPCC
  - rFVIIa
- 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

Bleeding treatment PRIOR to ITI

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"

Recommended dosing: Either 3 x 90ug/kg or 1x270 ug/kg rFVIIa per bleed. Higher single dose may decrease the cost, early administration (<2h) decreases re-bleeding rate

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

Salaj et al., Haemophilia 2009, 15(3) 752-9

By-passing agents during ITI

By- passing agents during ITI CONTRADICTORY statements?

- **Prophylaxis during ITT using rFVIIa failed to show favourable results compared to aPCC**
  - » Brackmann et al., Blood Coagul Fibrinolysis, 2000
- **Prophylaxis with rFVIIa considerably reduced bleedings compared to previous treatment.**
  - **Eight/nine patients were satisfied or very satisfied with rFVIIa treatment**
  - **Subjective quality of life (QoL) was improved, much improved, or significantly improved**
    - » Morfini et al. Haemophilia 2007

Bleeding prevention during ITI Bypass therapy with aPCC

Bonn Protocol				
Scheme	Phase	FVIII U/kg	aPCC U/kg	Regimen
1*	1	100	50	BID until < 1 OU**
	2	150		BID until normal R/S
2		150		BID until normal R/S

* For patients with high bleeding tendency

** Oxford Units, correspond to about 2 BU

At the time of introduction of Bonn protocol aPCC was the only available bypassing agent

Oldenburg J. VOX SANG 1999; 77 Suppl 1:49-54.

Bleeding prevention during ITI with rFVIIa

First report

- **4 year boy, severe haemophilia A with inhibitors (116 BU peak)**
- **ITI (100 U/kg/d) rFVIII**
- **9 weeks with 19 severe bleeds, treated on demand (90µg/kg/d). Bleeds led to immobility (wheelchair)**
- **21 weeks on rFVIIa prophylaxis (90µg/kg/d) resulted in significant decrease of bleedings (7 bleeds) and return to kindergarten free of wheelchair**

Regiment	Ferequency of bleeds: Number/week	Days of immobility Days/week	Injections of rFVIIa Injections/week
On demand	2.1	6.0	8.4
Prophylaxis	0.4	1.1	7.8

- **Clinically proven longer biological effect of rFVIIa**
- **Improved mobility and increased QoL**

Saxon et al. Thromb Haemost 2001; 86: 1126–7

By-passing agents out of ITI

Bleeding prophylaxis in inhibitor patients

- **rFVIIa administered prophylactically can reduce bleeding rate in 46-52%**
  - **No matter what is the relation to ITI**
  - **In adults and children**
  - **At median individual dose of 133-165 ug/kg**
  - **At dosing frequency from 3-7 /week**
  - **No thrombotic complication**
    - » Young et al.,Thrombosis research 2012
- **aPCC prophylaxis is well tolerated in children, even when failed ITI**
  - **60-100 IU aPCC/dose on different dosing regimens based on bleeding patern**
  - **Mean annual bleeding rate of 1,5/year**
  - **No serious thrombotic complications (only associated with venous access)**
    - » Ettinghausen et al. Haemophilia 2010 16(1) 90-100

On-demand treatment for inhibitor patients

- **rFVIIa**
  - **3x90 or 1 x 270 ug/kg**
  - **See comments related to "prior ITI"**
  - **More convenient**
  - **Safe**
- **aPCC**
  - **50-100 IU/kg**
  - **Many decades of experience**
  - **Less convenient (?)**
  - **Safe (?)**
- **Non responsive bleedings?**
  - **Combination/alteration of rFVIIa and aPCC**

SUMMARY I

Bleeding prevention and treatment <u>prior</u> to ITI

- **International Consensus for ITI recommends rFVIIa for treatment of bleeding episodes in haemophilia patients planning to undergo ITI**
- **rFVIIa may improve the success of ITI by decreasing and maintaining low inhibitor titres prior to initiation of ITI**
- **Avoiding anamnestic response should be the goal of therapy prior to ITI as it will increase the success rate and cost-effectiveness of ITI.**

SUMMARY II

Bleeding prevention and treatment during/after ITI

- **Bypassing agents (both aPCC and rFVIIa) are recommended for the treatment of bleeding episodes during ITI.**
- **aPCC has been used in that way for many decades succesfully and safely**
- **Latest reports confirm that rFVIIa is effective and safe for prophylaxis during ITI, decreasing the frequency of bleeds and increasing QoL**
- **rFVIIa is recombinant and thus carries no known risk of any blood born infections and thus might be the treatment of choice for all „plasma naive“ children with inhibitors**