"Brno protocol" - case report

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Family and personal history

- **Boy with severe FVIII deficiency**
  - **Pre-natal diagnose**
  - **Grand father with the same mutation also developed HR inhibitor.**
    - Type of the mutation: Nonsense mutation in Exon 14: 1047 His-Tyr
  - **Mother wished to continue with the pregnancy**
- **Development of inhibitors (iFVIII) after 4 doses of pdFVIII**
  - **Early introduction of FVIII (bleeding from ubilical cord)**
  - **Combined danger signals**
    - These were: early and high peak treatment on demand, vaccination

Risk factors for ITI

- **Historical inhibitor titre peak before ITI 166 BU**
- **ITI started at 2 years of age (waiting for 12 Mo did not decrease his iFIII<10BU despite rFVIIa only treatment)**
  - **Starting inhibitor titre 17 BU**
  - **Max on-ITI inhibitor titre 7373 BU!!!**
- **High risk ITI commenced**
  - **200 IU/kg/d FVIII (pdFVIII on which iFVIII developed)**
  - **Scheduled for up to 3 years**

ITI protocol used

- ***Primarily*** **Modified Bonn protocol**
  - **200 IU pdFVIII/kg/day in single i.v. bolus**
  - **No aPCC**
  - **When bleeding – on demand rFVIIa 90 - 120 ug/kg**
    - Often 1 – 3 doses/bleed
- **Effect:**
  - **After one year of ITI iFVIII dropped down to 115 BU**
  - **Two years from the start of ITI iFVIII 1-10 BU**

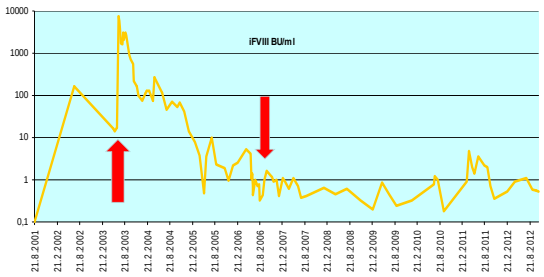
After 2 years of HD ITI

- iFVIII still between 1-10 BU
  - Increased physical activity led to repeated TRAUMA bleeds treated with rFVIIa „on demand“
  - Lower QoL, high expenses

ITI regimen modified after 2 years

- **„Brno protocol“**
  - **pdFVIII 200 IU/kg/day in one single i.v. bolus**
  - **Bleeding prophylaxis with rFVIIa 160 µg/kg/day in one single i.v. bolus**
    - After initial 3 Mo rFVIIa tappered down to 90 ug/kg/day
- **Effect:**
  - **QoL increased**
  - **iFVIII oscillating between 0,4 – 10 BU**
  - **No spontaneous bleeding episodes**
    - In total bleedings comparable to other HA children WITHOUT inhibitors
  - **Costs comparable to „on demand“ treatment with rFVIIa**

iFVIII development during ITT
(from start of ITT to antiCD20 application)



ITI augmented with Rituximab

- **After 3 years still LR inhibitors ⟶ Rituximab (antiCD 20) added**
  - **After 1 course of antiCD20 375 mg/kg 1x per week x 4**
    - Recovery FVIII 54%
    - FVIII constantly over 2%
    - T1/2 2,7 h
    - **rFVIIa prophylaxis stopped**
  - **6 months after antiCD20 (Rituximab)**
    - Negative inhibitors
    - Recovery 79%, T1/2 6,5 h
      - "Border-line" results. Would meet "I-ITI criteria" for tolerance, but would not be considered tolerant e.g. in Frankfurt

What happened further…..

- **After finishing his ITI, switched to standard prophylaxis**
- **Since that time no serious bleeds, no need for by-pass treatment**

- **However:**
  - **After 5 years again increased iFVIII (LR, max 4,8BU)**
  - **Second attempt of ITI (4/11 – 3/12)**
    - LD 65IU/kg on alternate days, no by-pass needed
    - Second antiCD 20 course 6/11 (very short 5-6Mo response)
  - **Still on LD ITI/HD prophy since that time**
  - **Continuous need for CVAD**
  - **Lower QoL due to frequent injections and visits to CCC**
    - Psychological and family related problems as well

Currently…

- **Currently**
  - **Since last LD ITI never completely free of inhibitor**
    - Inhibitors between 0,5 – 1,5 BU
    - His recovery has not exceeded 66,5% and half life is around 6 – 6,5 h
    - However no need for by-pass nor any major bleeds
  - **On medication from psychologist/psychiatrist**
  - **Septic CVAD pulled out in March**
    - iFVIII 1,5 BU after the surgery
  - **LD ITI/HD prophy 50 IU/kg on alternate days**
  - ***His brother has no inhibitors after >100 ED***

Summary

- **Every patient is "unique"**
- **Try to avoid danger signals**
- **Prevention of iFVIII is better/cheaper than the treatment**
- **High risk patients need HD ITI**
  - **Success rate up to 80%**
  - **Relapse rate over 12%**
- **I-ITI study "tolerization" criteria might be too weak?**
- **Never stop prophylaxis in patient after ITI**
- **Observe such a patient closely for the rest of his life**
  - **Compliance is one of the crucial issues**