“Brno protocol” - case report

published in Haemophilia 2008, 14, 1140–1142

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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
  – 280 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 tapered 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 "1-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 ITIHD prophyl 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 prophyl 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%
- 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