Challenges and Strategies in the management of patients with Haemophilia and Inhibitors
A South African Experience

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Introduction

• South Africa: a brief perspective of haemophilia care

• Challenges and Strategies
  • Prevention
  • Management

• An illustration from Limpopo Province

• The future
Inhibitors in Haemophilia

- Affect about 20-30% of people with severe haemophilia A
- And 3-5% of people with haemophilia B

- Usually develop within the first 20 exposures to clotting factor concentrate
- High titre $\geq 5$ BU/ml, low titre $< 5$ BU/ml
- High responder, low responder
Haemophilia in South Africa

Expected Epidemiology

- About $10^6$ births/year
- 100 boys with haem/year
- 5000 PWH in total
- Haem A:B = 4:1
- 80 haem A/year
- Fewer than half severe
- Expected inhibitor incidence approx 10/yr

Reality

- Reported data often incomplete
- Approximately 80 new cases per year
- About 2500 PWH in total
South Africa an economic perspective

Source: District Health Barometer 2013-14
Haemophilia in Limpopo

• Haemophilia Treatment Centre opened in 2000
  
  • Serves approximately 120 patients with Haemophilia A
  • 2001-2015: 4 fold increase in CFC use
  
  • About half of those 120 diagnosed with severe HA in early childhood since clinic started
  • Standard of care is episodic / on demand factor replacement
  • Just under 20% have developed high titre inhibitors
Haemophilia in Limpopo

• Two brothers diagnosed at 2 and 10 years with severe haemophilia A.
  • Live in a rural village
  • Travel times to HTC can be lengthy

• Both developed inhibitors within 20 EDs
  • Older brother first titre 9 BU, repeat 24 BU
  • Younger brother first titre 1 BU, rose to 9 BU

• Q1: Could this have been prevented?

• Q2: Now what?

Case information used with consent
Challenges and Strategies: Prevention

- Modifiable causes of inhibitors may include
  - Nature of CFC
  - Timing and dose of administration of CFC

- RODIN and SIPPET study (results of latter pending)
  - pdFVIII vs rFVIII
  - No significant difference in inhibitor development shown

- CANAL and RODIN study
  - Intense exposure a risk factor
  - Prophylaxis protective

- Low dose prophylaxis & EPIC study
  - Conflicting results regarding the protective effects of low dose prophylaxis together with avoidance of immunologic danger signals
  - Kurnik K et al. *Haemophilia* 2010:16:256-62
Challenges and Strategies: Treatment

- Two main strategies:
  - Immune tolerance induction (High dose vs low dose)
  - Bypass agents
    - rVIIa
    - APCC

- Both very costly: test the limits of affordability

- For low titre inhibitors FVIII at 2-3x standard dose an option
Challenges and Strategies: Treatment

• International Immune Tolerance Study

• High dose 200IU/kg/day and low dose 50IU/kg 3x/week
  • Both arms achieved similar rates of immune tolerance
  • High dose achieved tolerance slightly faster
  • More bleeding events in low dose cohort

• Hay CRM, DiMichele DM. *Blood* 2012 119:1335-1344
Challenges and Strategies: Treatment

- Strategy = ITI

- Select good risk patients only
  - Titre < 10 BU at start of ITI
  - Historic peak < 200 BU/ml
  - Within 5 years of diagnosis

- Low dose protocol affordable (?) and most practical accepting possible increased bleed rate
  - 150 IU/kg/week (factor in an up to 50% failure rate)
  - Once tolerized need prophylaxis 75 IU/kg/week
Challenges and Strategies: Treatment

- Strategy no/failed ITI

- Bleed Prevention
  - Target joint

- Try to limit treatment to a single dose of bypass agent
  - Reduce time to treatment
  - Hospitalize for supervision and rehabilitation

- Monitor inhibitor levels: use FVIII when low titres allow
The Future

- Steadily increase the procurement of CFCs for prophylaxis and ITI
- Identify strategies to reduce the time to treatment for patients on therapy with bypassing agents
- Progressive realization of equal access to healthcare
- Availability of more cost-effective medicines

Thank you