Inhibitors in Mild Haemophilia

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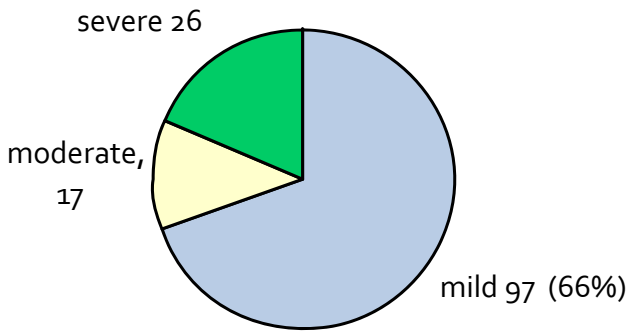
Mild Haemophilia

- Normally defined as factor VIII levels 5 - 40 IU/dL
- Proportion of patients with mild HA varies between centres
  - 32% patients with mild HA in a large international review
  - 50% of pts in Canadian and Spanish registries
  - 16% of pts in registry involving mainland China

- Stonebraker JS et al. A study of variations in the reported haemophilia A prevalence around the world. Haemophilia 2009.
- Aznar JA et al The national registry of haemophilia A and B in Spain: results from a census of patientsHaemophilia 2009; 15 1327–30.
- Poon MC, Luke KH. Haemophilia care in China: achievements of a decade of World Federation of Hemophilia treatment centre twinning activities. Haemophilia 2008; 14: 879–88.

Haemophilia A patients: Royal Adelaide Hospital



Data analysis Jan 2010

Total 140

Inhibitors in MMHA

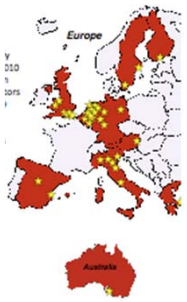
How common a problem?

- Early studies suggested 3 to 13% individuals with MMHA have inhibitors
- UKHCDO data between 1990 and 1997, 28% (15/57) new inhibitors occurred in patients with mild or moderate haemophilia.
  Hay et al. Thromb Haemost 1998; 79: 762–6
- Annual incidence
  - 3.5 per 1000 patients registered with severe haemophilia
  - 0.84 per 1000 for patients with mild / moderate HA.
- South Australia 9/129 individuals - incidence 6.9%

1. Lusher JM et al N Eng J Med 1993; 328: 453-9.2.
2.Sultan Y et al Thromb Haemost 1992; 67: 600-2.6.
3.Rizza CR et al British Medical Journal 1983; 286: 929-32.

INSIGHT Study

- 11 countries, 34 HTCs
- 33 European, 1 Australia
- 2695 pts
- 1327 genotyped (49%)



INSIGHT study - Incidence

- Retrospective data collection on individuals treated between 1980 and 2010

	N or Median	% or IQR
Caucasian ethnicity	2557	95%
Baseline FVIII:C	10	16-18
Moderate pts	641	24%
Age at Inclusion Age at End FU	8 36	0-26 18-55
ED to FVIII	23	8-75
Inhibitor Present	**111**	**4%**

Clinical Characteristics

- Development of "severe" bleeding pattern
  - 2/3 pts exhibit bleeding pattern similar "acquired haemophilia"
  i.e. mucocutaneous bleeds, severe GI bleeding, urogenital bleeding

  Hay et al. Thromb Haemost 1998; 79: 762–6
- Failure of response to standard therapy –often post surgical
- Routine surveillance

Inhibitor Activity

Inhibitor targets autologous (own) and allogeneic (transfused) FVIII

Associated with a drop in baseline FVIII levels – change in bleeding pattern

- 22/26 pts

  Hay et al Thromb Haemost 1998; 79: 762–6
- 13/14 pts
  - 6 had FVIII:C levels between 2 to 8 IU/dL
  - 7 had <0.01 IU/dL

  Mauser-Bunschoten et al Haemostasis 2011; Epub Aug

Antibody Characteristics

Activity against allogeneic (transfused) FVIII only

- Number of reports where inhibitor has no activity against own FVIII.
- Also individuals reported where change in inhibitor activity
  - Return of FVIII levels back to "baseline" despite persistent inhibitor
  - Not just related to change in inhibitor level (titre)
  - Speculated change due to development of tolerance to self.

1. Peerlinck et al Blood 1999 93: 2267-2273
2. Santagostino. Thromb Haemost 74:619, 1995
3. Fijnvandraat. Blood. 1997 89: 4371-4377

Clinical and Lab Characteristics

Age at diagnosis

- Median age ranged from 33 to 66 yrs (South Australia 50 yrs age)

Exposure Days (ED) at diagnosis

- Average 5.5 bleeding episodes at time of inhibitor development
- 30-40% individuals will develop inhibitor after > 50 ED (SA mean 48 ED)

Inhibitor Titre

- Median level at diagnosis ranges from 2.3 to 11.6 BU
- Median peak level ranges from 5 to 23 BU

Hay et al Thromb Haemost 1998; 79: 762–6
Mauser-Bunschoten Haemostasis 2011; Epub Aug

Mortality Risk

INSIGHT study

- Overall 138 deaths in 2695 pts = 5.1%
- 16 deaths in 111 pts inhibitors = 14%, Adjusted HR 2.2 (CI 1.3 – 3.8)
- Inhibitor present in 44% pts at time of death

- Directly contributed to 4 deaths (3 bleeds, 1 infective)

- Tolerisation attempted in equal number dead/surviving pts

Natural History Inhibitors in MMHA

UKHCDO series

- **10/26 (40%)** disappeared spontaneously
  - median time to disappearance 9 months
  - no recurrences during a median FU 3 yrs follow up
  - no data given on re-exposure to FVIII
- ITI attempted in 8 individuals – successful eradication in 2
- Persistent inhibitor in 14/26 (55%) after a median FU 99 mths.

Risk factors for Inhibitor Development

- Genetic
- Environmental

Genetic Risk Factors for Inhibitors in MMHA

- Clustering mutations in A2 domain and the C1- C2 junction.
- Specific mutations
  Arg593Cys, Arg2150His, Trp2229Cys, Tyr 2105Cys
- Often involve the introduction of a new cysteine residue,

Peerlinck K, et al. Blood 1999; 7: 2267-73
Oldenburg J, et al.Haemophilia 2006; 12 (Suppl. 6): 15-22
Jacquemin M, et al.J Thromb Haemost 2003; 1: 456-63

Genetic risk factors –INSIGHT data

Location FVIII gene mutation

92% (71/79) pts inhibitors had missense mutations in two regions:

- Amino acids 531 – 668 (A2 domain; 6 separate locations)
- Amino acids 1761- 2333 (A3,C1, C2 domains; 19 separate locations)
- 62% of all individuals genotyped had defects in this region
- Inhibitor prevalence in 71/825 = 9%

Adjusted HR 5.2 (95% CI 2.5-11.0)

Positive family history – 12/49 inhibitor present

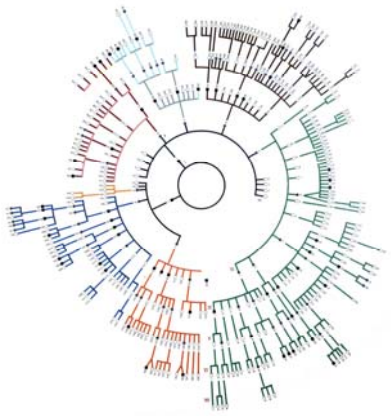
Adjusted HR 3.6 (95% CI 1.7-7.6)

Cysteine replacement

Adjusted HR 1.8 (95% 1.1-2.8)

Specific High Risk FVIII mutations

Arg 2150 His



Specific High Risk FVIII mutations

Arg 2150 His

- SA Inhibitor rate = 21%, OR = 12.8 (95% CI 2.4 – 67)
- INSIGHT data 14/77 pts = 23%, Adjusted HR 2.6 (1.5-4.7)
- Initial low FVIII level, normally return to baseline level

Tyr 2105 Cys

- High risk of inhibitor formation > 50%
- Occurs after limited exposure – normally second
- Severe phenotype –fatal spontaneous bleeding reported

Environmental Risk Factors

Intensive or Peak Exposure

- Hay et al noted 16/26 cases associated with recent intensive treatment
- Canadian paediatric data
  - All patients developing inhibitors did so after peak treatment period
- Dutch paediatric centre
  - First intensive treatment for surgery Adjusted RR 186 (25-1403)
- Intensive FVIII exposure
  - > 30 years of age OR 13.54 (2.7-57)
  - < 30 years of age OR 1.55 (0.6-10)

Sharathkumar A J Thromb Haemost 2003; 1: 1228–36
Koestenberger M, Leschnik B et al. J Thromb Haemost 2004; 2: 676
Kempton CL J Thromb Haemost 2010; 8: 2224–31.

Treatment Options

- Watch and wait
  - On-demand treatment with bypassing agent
  - Avoidance of re-exposure to FVIII
  - Use of desmopressin (DDAVP)
- Immunosupression alone
  - Mabthera
- Tolerisation with FVIII

Decision likely to be influenced by clinical scenario at presentation

Mabthera Experience

Anecdotal evidence

Franchini et al Haemophilia (2008), 14, 903–912

- Mild HA 9/13 cases reported responded to Mabthera 70%
- As opposed to ~ 50% response rate overall

Still concerns re long-term S/E

Unclear optimal dosing schedule

Conclusions re inhibitors in mild HA

- Genotyping has a role in defining risk
- Advanced plan to minimise exposure in at risk patients
  - DDAVP
  - ? Use combination DDAVP/FVIII for surgery
- ? Avoid FVIII in very high risk pts e.g. Tyr2105Cys
- Data pending on environmental risk factors
- Data pending on best treatment options