Inhibitors in Mild and Moderate Haemophilia

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SA Pathology
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

2013-2014 data

- 65% Mild
- 25% Moderate
- 10% Severe

989 / 1533 patients have mild disease
Adult patients with Haemophilia A in SA
Phenotype of Mild Haemophilia

Ankle Arthropathy in MMHA

Ling et al.

Thromb Haemost 2011; 105: 261–268
Case Presentation

- 45 yr old male Mild HA
- Baseline FVIII level 6%
- Ongoing bleeding post-haemorrhoidectomy
- Failure to increment to FVIII replacement therapy
- Baseline FVIII 6%, FVIII inhibitor level 7 BU
- Mutation Arg 2150 His
Inhibitors in MMHA

How common a problem?

- Early estimates varied from 3-13% MMHA patients have inhibitors

- UKHCDO data 1990 -1997
  - 28% (15/57) new inhibitors occurred in pts with MMHA


- Annual incidence – PTP (severe) and MMHA
  - 3.5 per 1000 patients registered with severe haemophilia
  - 0.84 per 1000 for patients with mild / moderate HA.

Familial Predisposition

INSIGHT study

- **International Study** on etiology of inhibitors in patients with a mild or moderate form of hemophilia A influence of Immuno Genetic & Hemophilia Treatment factors.

- Aims – Size (Incidence) and Cause (Aetiology) problem
INSIGHT Study

- 11 countries, 34 HTCs
- 10 European, 1 Australia
- 2695 pts
- 49% genotyped
INSIGHT study - Incidence

- Retrospective data collection on pts treated between 1980 and 2010

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<thead>
<tr>
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<th>N or Median</th>
<th>% or IQR</th>
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<td>Caucasian ethnicity</td>
<td>2557</td>
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<td>Baseline FVIII level</td>
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<td>16-18</td>
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<td>Inhibitor Development</td>
<td><strong>111</strong></td>
<td><strong>4%</strong></td>
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</table>
Overall incidence

- 109/2711 pts = 4.0%

Risk related to number ED

- Mean ED = 28 d
- 17/58 cases occurred between 50 and 100 ED

Eckhardt et al. BLOOD 2013
Clinical Characteristics

- Development of “severe” bleeding pattern
  
  Due to activity against autologous and allogeneic FVIII


- 13/14 pts  Mauser-Bunschoten et al Haemostasis 2011; Epub Aug
  - 6 pts FVIII:C levels between 2 to 8 IU/dL
  - 7 patients <0.01 IU/dL

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

Clinical Characteristics

No inhibition of brothers FVIII activity

Arg2150His

Peerlinck et al Blood 1999 93: 2267-2273
Clinical Characteristics

- Failure of response to standard therapy
  - post surgical
  - post bleed

High index of suspicion required if sub-optimal response to therapy

- Routine surveillance
Clinical and Lab Characteristics

Age at diagnosis
- Older - Median age 33 to 60 yrs

ED at diagnosis
- 5.5 bleeding episodes (range 1-107).
- 30% to 40% patients have > 50 ED at diagnosis

Inhibitor titres
- At diagnosis - Median 11.6 BU/ml (range 0.5-568)
- Peak - Median 22.5 BU/ml (range 1.1-1000)

Mauser-Bunschoten Haemostasis 2011; Epub Aug
Median peak inhibitor titre 9 BU mL⁻¹ (IQR, 2–30)

36 (61%) patients had a high titre inhibitor.

FVIII was decreased in 56% inhibitor patients; ≤2% in 36%

30 (51%) patients had an increased bleeding tendency

47 (80%) patients needed treatment for bleeding
Mortality rate increased 5.6 fold
- 15% versus 5% in the study period

10 patients inhibitor present at time of death

Bleeding event contributed to death in 7/10
- GI haemorrhage
- Intracranial bleed
- Retropharyngeal

Majority of patients with MMHA will have missense mutations. Missense mutations associated with lower inhibitor risk ~ 5%

Genetic Risk Factors for Inhibitors in MMHA

- Clustering mutations in A2 domain and the C1-C2 junction.
- Specific mutations
  Arg593Cys, Arg2150His, Trp2229Cys, Tyr2105Cys
- Often involve the introduction of a new cysteine residue.

Point mutation location in MMHA and inhibitor risk

<table>
<thead>
<tr>
<th>Mutation location</th>
<th>Inhibitor rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1/C2 domains</td>
<td>7.1%</td>
</tr>
<tr>
<td>Non C1/C2 domains</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Amino-acid change

<table>
<thead>
<tr>
<th>Amino-acid change</th>
<th>Inhibitor rate</th>
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<tbody>
<tr>
<td>Change in class</td>
<td>7.1%</td>
</tr>
<tr>
<td>No change in class</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Mutation location – INSIGHT

231 mutations identified
19 associated with inhibitors

Confirmed location of at risk mutations in A2 and C1/C2 domains

Identified further at risk mutations in the A3 domain
## Genotype and inhibitor risk - INSIGHT

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Pts</th>
<th>No inh (%)</th>
<th>Incidence 20 d</th>
<th>Incidence 50 d</th>
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</thead>
<tbody>
<tr>
<td>Arg531Cys</td>
<td>35</td>
<td>1 (2.9)</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Arg593Cys</td>
<td>104</td>
<td>12 (11.5)</td>
<td>9.3%</td>
<td>18.5%</td>
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<tr>
<td>Asp2074Gly</td>
<td>11</td>
<td>3 (27.3)</td>
<td>21.2%</td>
<td>21.2%</td>
</tr>
<tr>
<td>Arg2150Cys</td>
<td>57</td>
<td>9 (15.8)</td>
<td>2.2%</td>
<td>12.2%</td>
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<tr>
<td>Arg2159Cys</td>
<td>21</td>
<td>3 (14.3)</td>
<td>9.1%</td>
<td>31.4%</td>
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<tr>
<td>Trp2229Cys</td>
<td>10</td>
<td>5 (50.0)</td>
<td>41.7%</td>
<td>41.7%</td>
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<tr>
<td>Phe1775Val</td>
<td>3</td>
<td>2 (66.7)</td>
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<td></td>
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<tr>
<td>Phe2101Cys</td>
<td>2</td>
<td>2 (100)</td>
<td></td>
<td></td>
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<tr>
<td>Tyr2105Cys</td>
<td>6</td>
<td>3 (50)</td>
<td></td>
<td></td>
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Eckhardt et al BLOOD Prepublished online August 7, 2013
Family with Arg2150His mutation

Hunt Family Tree - Haemophilia A
Arg2150His/Cys

- The South Australian (HUNT family) mutation
- Reduced FVIII levels at presentation that return to baseline
- Rarely severe bleeding phenotype
- Subsequent DDAVP response
- Amnestic response with re-exposure

SA Inhibitor rate in Arg2150His mutation = 21%

INSIGHT data 14/77 pts = 23%
Tyr2105Cys Mutation

- Development of severe bleeding phenotype
- Typically after 2\textsuperscript{nd} significant exposure to FVIII
- “Acquired type” phenotype with mucosal, oral bleeds and undetectable FVIII:C

Evaluated patients with MMHA with “peak” exposure

2 patients / 48 developed inhibitors ~ 4%

Both mutations known to be associated with inhibitor formation

Lower risk than previously described


- Case-control study from a number of adult sites
- 36 cases, 63 controls
- Intensive FVIII exposure
  - > 30 years of age OR 13.54 (2.7-57)
  - < 30 years of age OR 1.55 (0.6-10)
- No association with CI
- No reduction in risk formation if >50 exposure days

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<thead>
<tr>
<th></th>
<th>Inhibitor Pos</th>
<th>Inhibitor Neg</th>
<th>P-value</th>
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<tr>
<td>Age at 1st exposure</td>
<td>43 yrs</td>
<td>6.7 yrs</td>
<td>&lt;0.01</td>
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<tr>
<td>Age at 1st peak</td>
<td>53 yrs</td>
<td>21 yrs</td>
<td>&lt;0.01</td>
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<td>Age at peak leading inhib</td>
<td>66 yrs</td>
<td>27 yrs</td>
<td>&lt;0.01</td>
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<tr>
<td>Cl infusion exposure</td>
<td>37%</td>
<td>31%</td>
<td>0.62</td>
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E. P. Mauser-Bunschoten, Haemophilia (2012), 18, 263–267
<table>
<thead>
<tr>
<th>Pt No</th>
<th>Severity</th>
<th>Mutation</th>
<th>ED prior</th>
<th>Age (yrs)</th>
<th>Initial level (BU)</th>
<th>Highest level (BU)</th>
<th>Duration (months)</th>
<th>Current status</th>
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<td>Arg2150His</td>
<td>26</td>
<td>50</td>
<td>3.6</td>
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Mean ED 48 days, > 50 days in 3 patients

Mean age 44 yrs, median age ~ 50 yrs age
Treatment of “at risk” patients

**Very high risk group**
- ? Avoidance of FVIII
- Up front use of bypassing agents if severe bleed

**High risk group**
- Where possible use DDAVP
- Combination Rx for more major bleeding / surgery
  - DDAVP, anti-fibrinolytic therapy, FVIII
Strategies to minimise FVIII exposure

- Use of DDAVP where possible
- Use of tranexamic acid – alone or as adjuvant
  Endoscopy without factor replacement
  Davis et al. Haemophilia 2013; 19: 583

- Novel therapies – non-FVIII molecules
  Muto et al. BLOOD Nov 2014
DDAVP response

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<th>Moderate, n (%)</th>
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<td>Responder</td>
<td>49 (80.3)*</td>
<td>1 (7.7)</td>
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<tr>
<td>Partial responder</td>
<td>7 (11.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>5 (8.2)</td>
<td>12 (92.3)</td>
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<tr>
<td>Total</td>
<td>61 (100)</td>
<td>13 (100)</td>
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DDAVP response by mutation

DDAVP response in mild HA + inh
DDAVP Response – RISE study

? Worth trying in moderate HA

RISE study

- 81 patients with moderate HA
- Median response 18 IU/dL

- CR in 2 (2%) patients
- PR in 19 (15%)

Loomans ISTH ABSTRACT 2015
Management of inhibitors

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

- Immunosuppression alone
  - Mabthera

- Tolerisation with FVIII

Decision likely to be influenced by clinical scenario at presentation
Eradication of Inhibitors - INSIGHT

- **Eradication Treatment**
- **No Eradication Treatment**

- **Inhibitor Disappearance**
  - Eradication Treatment: 70%
  - No Eradication Treatment: 60%

- **Sustained success**
  - Eradication Treatment: 90%
  - No Eradication Treatment: 60%
Rituximab and Inhibitors in MMHA

- Retrospective review, single centre.
- Identified 9 pts with MMHA + inhibitors Rx with Rituximab.
  - 375 mg/m² x 4 weeks
- All treated within first 2 months after detection

Rituximab and Inhibitors in MMHA

- All 9 patients responded
- Median time to response 95 days
- 8 patients re-exposed to factor VIII
- Only 2/8 developed recurrence – low titre
- ? Standard of care

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

- ? Early use of Rituximab after inhibitor detection
  - more data needed on response according to genotype
4. Inhibitors and mild hemophilia A

- In mild hemophilia
  - All patients should have their mutation identified
  - All patients exposed to FVIII concentrate should have an inhibitor test at 6 weeks or earlier if bleeding occurs
  - A FVIII inhibitor should be excluded before surgery
  - The Bethesda assay should be used to detect inhibitors

Recommendations ISTH FVIII SSC