Challenges when people with haemophilia develop inhibitors

Huyen Tran
Haemophilia Treatment Centre, The Alfred, Melbourne
Australian Centre for Blood Diseases, Monash University
Short clinical review

- Inhibitor development and treatment
- New data on inhibitors
- Surgery in inhibitors (context of emicizumab)
Factors influencing inhibitors

Patient genetics:
- Type of mutation
- MHC class I/II genotype
- Race
- FHx
- Polymorphic genes of cytokines

Patient environment:
- Age of first infusion
- Immune system challenges

Treatment:
- Type of factor quantity

Inhibitors
Inhibitor Project

Methods/Results

Cumulative incidence of Inhibitor Development

% Inhibitor Development

Exposure days
Inhibitor status of HA patients in Australia

• Incidence
  • Severe HA, 27%
  • Non-severe, 8%
  • Paediatrics, 71%

• Likelihood for tolerisation for patients with inhibitors,
  • Severe 63% vs non-severe 0%

• Inhibitor no longer present, 78% had tolerisation

McRae et al., Blood congress 2018
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Severity</th>
<th>Gender</th>
<th>Age</th>
<th>Genetic Mutation</th>
<th>Current Inhibitor Status</th>
<th>Titre Level</th>
<th>Time on Tolerisation</th>
<th>Product</th>
<th>BPA-FEIBA</th>
<th>BPA-Novoseven</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia B</td>
<td>Severe</td>
<td>Male</td>
<td>31</td>
<td>Not tested</td>
<td>On ITT - Previously Tolerised High Responder</td>
<td>High</td>
<td>7years 5months</td>
<td>Monofix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vWD Type 3</td>
<td>Severe</td>
<td>Male</td>
<td>16</td>
<td>Missense Mutation</td>
<td>On ITT</td>
<td>High</td>
<td>3years 5months</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>13</td>
<td>Large Deletion</td>
<td>On ITT - Previously Tolerised High Responder</td>
<td>High</td>
<td>6years 6months</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>42</td>
<td>Intron 22 Inversion - Distal</td>
<td>On ITT</td>
<td>High</td>
<td>4years 2months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>52</td>
<td>Intron 22 Inversion - Distal</td>
<td>On ITT</td>
<td>High</td>
<td>2years 4months</td>
<td>Advate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>74</td>
<td>Large Deletion</td>
<td>On ITT - Previously Tolerised High Responder</td>
<td>High</td>
<td>6years 5months</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>8</td>
<td>Not tested</td>
<td>Tolerised</td>
<td>Low</td>
<td>3year</td>
<td>Advate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>7</td>
<td>Nonsense Mutation</td>
<td>On ITT</td>
<td>High</td>
<td>2years 6months</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>7</td>
<td>Intronic 22 Inversion</td>
<td>On ITT</td>
<td>High</td>
<td>5years 4months</td>
<td>Biostates</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>6</td>
<td>Intronic 22 Inversion - Proximal</td>
<td>On ITT</td>
<td>High</td>
<td>5years 10months</td>
<td>Biostates</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>6</td>
<td>Intronic 22 Inversion</td>
<td>On ITT</td>
<td>High</td>
<td>4years 5months</td>
<td>Biostates</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>6</td>
<td>Nonsense Mutation</td>
<td>On ITT</td>
<td>High</td>
<td>5years 5months</td>
<td>Biostates</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>8</td>
<td>Hemizygous Frameshift Mutation</td>
<td>Tolerised</td>
<td>Low</td>
<td>3year 4months</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>4</td>
<td>Not tested</td>
<td>On ITT</td>
<td>High</td>
<td>4years</td>
<td>Biostates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>4</td>
<td>Deletion leading to Frameshift Mutation</td>
<td>Tolerised</td>
<td>Low</td>
<td>5months</td>
<td>Advate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>3</td>
<td>Not tested</td>
<td>On ITT</td>
<td>High</td>
<td>2years 5months</td>
<td>Biostates</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>3</td>
<td>Intronic 1 Inversion</td>
<td>On ITT</td>
<td>High</td>
<td>2years 5months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>3</td>
<td>Large Deletion</td>
<td>On ITT - Previously Tolerised High Responder</td>
<td>High</td>
<td>8months</td>
<td>Biostates</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>2</td>
<td>Not tested</td>
<td>Tolerised</td>
<td>Low</td>
<td>1year</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>5</td>
<td>Not tested</td>
<td>On ITT</td>
<td>High</td>
<td>1year 9months</td>
<td>Advate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>1</td>
<td>Not tested</td>
<td>Tolerised</td>
<td>High</td>
<td>8months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>2</td>
<td>Not tested</td>
<td>On ITT</td>
<td>High</td>
<td>3year 6months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>1</td>
<td>Large Deletion</td>
<td>On ITT</td>
<td>High</td>
<td>3year 4months</td>
<td>Biostates</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>48</td>
<td>Intronic 22 Inversion</td>
<td>On ITT</td>
<td>High</td>
<td>3year 2months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>Severe</td>
<td>Male</td>
<td>4</td>
<td>Frameshift Mutation</td>
<td>On ITT</td>
<td>High</td>
<td>8months</td>
<td>Advate</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
Inhibitor Project

Methods/Results

Time to Tolerisation

Number of patients

Duration

0-6mths  6mths-12mths  12mths-18mths  18mths-24mths  2yrs-3yrs  3yrs-4yrs  4yrs-5yrs  5yrs-6yrs  6yrs-7yrs  7yrs-9yrs

Low Titre  High Titre
Inhibitor Project

Methods/Results

TAC Report

Events

Timeline

Advate
Novo7

FEIBA?
Biostate

ITF
Rituximab

Sumit PARIKH, PhD (Health Informatics)
ABDR Senior Research Fellow
David believes there are many common misconceptions about haemophilia. “People think when they touch you, you’ll bleed”, he says. David notes there is usually “no rhyme or reason” why bleeds happen. He would rarely get a bleed when he was active or playing sports, but would then get one simply tripping on a step.

According to David, the more knowledgeable people are about haemophilia, the better off the patient community would be. He wishes the general public would “treat us like real people”, noting that often when people find out someone has haemophilia, they tend to “wrap you in cotton wool” and “not want to bump you”, as they think “if you cut yourself, you’ll bleed to death”.

David acknowledges that there is no simple way of explaining haemophilia, but the more informed people become about the condition, the less hassle and misinformation there will be.

The job is not yet done on haemophilia

While David would typically experience 4-5 bleeds a year when he was younger, he says that he would never go to hospital for a bleed but would put up with the pain, which would in turn cause his condition to worsen. Now when he has a bleed, about once or twice a year, David immediately goes in to see his team at the Alfred Hospital – where he has been receiving treatment for over 30 years – for management and support.

David reflects on how the new treatments that have been developed over the years have made life more manageable for people with haemophilia. When he was younger, there were no options to inject or self-infuse Factor at home – but today, patients have much greater flexibility and choice of what is available for them.

Growing up in the 60s and 70s, David says there was “not a great deal of support” trying to manage his condition. But now, David says, receiving treatment at the Alfred is “like a family”, with everyone from the doctors, physios, nurses, social workers and the secretary, providing an important support network for him.

Although David acknowledges that treatment innovations and support services for haemophilia have greatly improved over time, he believes “we haven’t fixed it yet. It’s better, but there’s still more to do”. David says that unless there is a cure, people like him with haemophilia still need support and relief from the disease. Until then, the job is not done.

有限的意识与理解

“Keep going, don’t give up, don’t sit around and do nothing.”

痛苦，耐心与坚持

当被问及如何用三字来形容与血友病生活，David说：“痛苦，耐心，坚持”。

痛苦—因为人们都痛苦，有时是“痛苦难忍”。用10的量表来衡量（10是最痛苦的），David经历的痛苦大部分时间是2-3，但有时它可能会上升至6-7。

耐心—要通过持续的医院访问经历一生与血友病生活。

坚持—“继续前进，不要放弃，不要坐下来无所事事”。

血友病在三字

痛苦，耐心与坚持
Better Days Are Coming

I Am Confident That a Bright Future Awaits Me
Therapeutic options for patients with inhibitors

Non-factor replacement therapy

Emicizumab

Fitusiran (siRNA)

Tissue factor pathway inhibitor

Fitusiran & TFPI remain in clinical trials and has potential benefits for haemophilia B with inhibitors
DOB 16/06/14
Date of Diagnosis 20/09/2018
Severe Haemophilia A
Inhibitor detected 31/10/18

67 presentations to hospital post inhibitor detection over 104 days.
17 presentations to hospital post commencement of emicizumab over 106 days and NO BLEEDS

Courtesy of Dr Heather Tapp & Team
HAVEN-1: Comparison of emicizumab vs prior BPA treatment: treated bleeds* (September 8 2017 cut-off)

*Comparison with data obtained from the NIS
ABR; annulaised bleeding rate; BPAs, bypassing agents; NIS, non-interventional study

Mancuso ME et al. ASH 2017; poster 1071
Mean ABRs over time were consistent between studies, in children and adults with or without FVIII inhibitors.

ABRs* over consecutive 24-week treatment intervals by study

*Based on the calculated annualised bleed rate for bleeds treated with coagulation factors; †Only data for time intervals with ≥10 participants are reported
NE, not estimable
The proportions of participants with zero bleeds† increased over time

Proportion of participants with 0 or 1–3 bleeds† over time

*Only data for time intervals with ≥10 participants are reported
†Bleeds treated with coagulation factors
Over 99% of target joints resolved in patients on emicizumab prophylaxis

- Target joint resolution was defined as ≤2 spontaneous bleeding events in a 52-week period in a joint previously defined as a target joint\(^1\)
- 195 of 217 (90%) participants had no spontaneous or traumatic bleeding into a target joint while on emicizumab
- 498 of 519 (96%) of target joints had ≤2 spontaneous or traumatic bleeding events while on emicizumab

\(^1\)Target joints were defined as major joints (e.g. hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeding events occurred over a 24-week period. Target joint resolution was defined as ≤2 bleeding events in a 52-week period in a joint previously defined as a target joint

Statistically significant, clinically meaningful improvements in HRQoL and health status were seen with emicizumab prophylaxis versus no prophylaxis. 

Haem-A-QoL, Haemophilia-Specific Quality of Life questionnaire; Haemo-QoL-SF, Haemophilia-Specific Quality of Life Assessment for Children Short Form; HRQoL, health-related quality of life; QoL, quality of life

Fitusiran (siRNA-AT)

- Investigational RNAi Therapeutic for the Treatment of Hemophilia

- Subcutaneous administration
- Long duration of effect (4 weekly dosing)
- Synthetic siRNA – no inhibitors
- Prophylaxis for both HMA & HMB without and with inhibitors
  - Breakthrough bleeds can be safely managed with FC replacement
    - Thrombosis - rescue with antithrombin concentrate?
- Benefit for rarer bleeding disorders

Hemophilia A or B (including inhibitors), insufficient quantities of Xa are generated via the intrinsic pathway

- TFPI limits production of Xa from the extrinsic pathway
- Anti-TFPI (PF-06741086) enables Xa production from the extrinsic pathway, in part compensating for loss from intrinsic pathway
Is ITI still valid?

Pros

• Simple treatment of breakthrough bleeds

• Simple management for surgery

• (Rare) or long-term adverse effects of non factor replacement therapy unknown

Cons

• Treatment burden and cost

• Low efficacy among high-risk patients

• Uncertain strategy following success

Julie

Chris

“I want a clean, fair fight — ah, what am I saying? — just beat the heck out of each other.”
Patients with planned surgeries, with the exception of minor procedures, were excluded from both studies.

Unplanned emergency surgeries and minor procedures were performed in patients receiving emicizumab.

Perioperative management was at the investigator’s discretion based on individual clinical assessment, without specific guidance (per protocol) on surgical management provided.

- BPA dosing guidance provided during the studies was not specific for surgery, but for BPA use for any reason\(^1\).

Demographics and baseline characteristics
Patients undergoing surgical procedures from HAVEN 1 & 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HAVEN 1 N=17</th>
<th>HAVEN 2 N=5</th>
<th>Total N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age (years)</td>
<td>20.0 (12–75)</td>
<td>11.0 (3–12)</td>
<td>14.5 (3–75)</td>
</tr>
<tr>
<td>Hemophilia severity at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (5.9)</td>
<td>0</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (5.9)</td>
<td>0</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>15 (88.2)</td>
<td>5 (100.0)</td>
<td>20 (90.9)</td>
</tr>
<tr>
<td>Median (range) number of bleeds in the 24 weeks before study entry</td>
<td>12 (3–180)</td>
<td>5 (3–12)</td>
<td>11 (3–180)</td>
</tr>
</tbody>
</table>

- Unplanned emergency surgeries and minor procedures were performed in patients receiving emicizumab
- Perioperative management was at the investigator’s discretion based on individual clinical assessment, without specific guidance (per protocol) on surgical management provided
  - BPA dosing guidance provided during the studies was not specific for surgery, but for BPA use for any reason¹

¹. Callaghan MU, et al. Use of Bypassing Agents Prior to and Post Bypassing Agent Dosing Guidance During Emicizumab Prophylaxis: Analyses from the HAVEN 1 Study
All surgical procedures

- 29 surgeries
- 10 managed with prophylactic BPAs
  - 8 procedures led to no post-op bleeds
  - 2 procedures led to treated post-op surgical bleeds
- 19 managed without prophylactic BPAs
  - 14 procedures led to no post-op bleeds
  - 2 procedure led to treated post-op surgical bleeds
  - 3 procedures led to untreated post-op surgical bleeds

- 33 procedures in 17 patients in HAVEN 1
- 5 procedures in 5 patients in HAVEN 2

- Surgeries included
  - Tooth extractions (6)
  - CVAD procedures (13)
  - Other (10)

CVAD, central venous access device.
Tooth extractions

5 patients underwent 6 tooth extractions (all in HAVEN 1)

- Antifibrinolytics were used for:
  - 1 extraction managed with prophylactic BPAs, with 1 treated post-operative bleed
  - 3 extractions managed without prophylactic BPAs, with 2 treated post-operative bleeds
CVAD insertion, replacement or removal

13 procedures

31%

4 managed with prophylactic BPAs

- 4 procedures led to no bleeds
- 0 procedures led to treated post-op surgical bleed

69%

9 managed without prophylactic BPAs

- 8 procedures led to no bleeds
- 0 procedures led to treated post-op surgical bleeds
- 1 procedure led to untreated post-op bleed

10 procedures in 7 patients in HAVEN 1
3 procedures in 3 patients in HAVEN 2

CVAD, central venous access device.
9 patients underwent 10 other procedures

- **Right knee arthroscopy/ synovectomy/ debridement of arthrolibrosis and chondroplasty**
  - 12 year old patient in HAVEN 1
  - Prophylactic rFVIIa on day of surgery and one day post surgery (total dose 1016 µg/kg)
  - 1 post-operative bleed treated with rFVIIa; total cumulative dose for 15 days after surgery, 3326.3 µg/kg

- **Laparoscopic appendectomy**
  - 12 year old in HAVEN 2
  - Prophylactic aPCC (dose 2250 units, 49.8 U/kg) one day prior to surgery
  - No post-operative bleeds
## Major surgeries: synovectomy*

<table>
<thead>
<tr>
<th></th>
<th>Synovectomy</th>
<th>Synovectomy</th>
<th>Arthrofibrosis + chondroplasty + joint debridement + synovectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of prophylaxis</strong></td>
<td>Standard rFVIII</td>
<td>Standard rFVIII</td>
<td>rFVIIa</td>
</tr>
<tr>
<td><strong>Cumulative dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only pre-operative</td>
<td>55.0 U/kg</td>
<td>106.7 U/kg</td>
<td>170.2 μg/kg</td>
</tr>
<tr>
<td>Cumulative dose post-procedure</td>
<td>192.6 U/kg</td>
<td>–</td>
<td>4087.8 μg/kg</td>
</tr>
<tr>
<td>Number of total doses post-procedure, n</td>
<td>4</td>
<td>–</td>
<td>49</td>
</tr>
<tr>
<td>Total post-op days on prophylaxis or treatment</td>
<td>3</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Bleed due to surgery</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional medication</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adverse events of special interest</td>
<td>No TE or TMA</td>
<td>No TE or TMA</td>
<td>No TE or TMA</td>
</tr>
</tbody>
</table>

*There was one additional major surgical case of synovectomy, which was managed without prophylaxis*
Summary

- Inhibitors among PwHA remains an important morbidity

- Emicizumab reduces ABR over time and maintains a low bleed rate
  - (potentially other NFRT to follow)

- Carefully plan for surgery among patients with chronic inhibitors receiving emicizumab