EVOLUTION OF INHIBITOR TREATMENT

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February 16, 2016 – Brussels, Belgium

European Haemophilia Consortium Round Table on Inhibitors
Inhibitor Development:  
*Treatment complication*

- It is the most serious complication associated with the use of factor concentrates
- Neutralizes infused factor, rendering patients resistant to conventional replacement treatment
- Occurs in approximately *one third of previously untreated boys* affected with severe hemophilia A
- The risk of inhibitors is maximal during the *first 20-30 days* of exposure to FVIII
Inhibitor: Treatment complication

- One-third are transient and spontaneously disappears

- In the presence of a persistent high titer inhibitor, standard FVIII replacement therapy is no longer effective leading to recurrent joint bleeds

- Inhibitors lead to a relevant morbidity and chronic degenerative joint damage

- An increased mortality was seen in patients with inhibitors (five times increased mortality rate)

Hemophilia-related cost

- Median annual hemophilia-related cost for **non-inhibitor** patients was $63,935
- A wide distribution of annual haemophilia-related cost for **inhibitor** patients
- Median cost of $271,357

(Valentino et al, Haemophilia 2012; 18: 332-338)
Treatment Modalities

1. **Bleeding control**
   - Low titer (<5BU) $\rightarrow$ high dose FVIII concentrates
   - High titer ($\geq$5BU) $\rightarrow$ Bypassing agents

2. **Prophylaxis**

3. **Inhibitor eradication**
   - Immune tolerance induction (ITI)
Options for treatment of bleeding

• (Human) factor VIII
• Activated prothrombin complex concentrates (e.g. FEIBA)
• Recombinant factor VIIa (rFVIIa)
• Recombinant Porcine factor VIII
Prothrombin-complex concentrates  
\textit{(FEIBA)}

- Widely used dose: 80-100 IU/Kg, to be repeated 2-3 times at 8-10 hour intervals

- Effect can only be determined by clinical observation and no specific assay is available to evaluate its efficiency

- Anamnestic response can occur: they do contain traces of factor VIII

- Risk of thrombogenicity: particularly problematic in elderly patients
Recombinant activated factor VII
(rFVIIa)

- rFVIIa requires frequent administration (90 μg/kg at 4-6 hour intervals)
- Clearance particularly rapid in children
- Single doses of 270 μg/kg have also been reported to be effective in the prevention and treatment of joint hemorrhage
- Effect can only be determined by clinical observation and no standard assay is available
- Some reports of thrombotic episodes associated with treatment
- High cost
ORIGINAL ARTICLE

Porcine recombinant factor VIII (Obizur; OBI-1; BAX801): product characteristics and preclinical profile

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Introduction: Acquired haemophilia A (AHA) is a rare, often severe, auto-immune bleeding disorder caused by the development of inhibitory antibodies (inhibitors) to factor VIII (FVIII). Bypassing agents, recombinant activated FVII or activated prothrombin complex concentrate, are currently recommended as first-line treatments to control bleeding events in patients with AHA. Aim: A plasma-derived porcine FVIII (HyateC, Ipsen, UK) was used as a first-line treatment for AHA but was discontinued in 2004 due to viral safety concerns. A recombinant pFVIII (rFVIII), Obizur (OBI-1; BAX801), which is expected to have a similar efficacy profile to HyateC but with a superior safety profile was developed and recently approved by the US Food and Drug Administration for the treatment of AHA. Methods: Obizur manufacturing begins with the expression of B domain deleted rFVIII by genetically modified baby hamster kidney-derived cells. The final purified and lyophilized drug product has a negligible risk of viral contamination and contains no animal-derived plasma proteins. Obizur was evaluated for immunogenicity, tolerability, pharmacoekinetcis and bleeding times in preclinical models including in haemophilic dogs, cynomolgus monkeys and FVIII-knockout mice. Results: Preclinical animal studies show that the efficacy and immunogenicity of Obizur are similar to that of HyateC and that Obizur has a more favourable safety profile. Conclusions: Obizur is a highly purified recombinant porcine FVIII drug product that has been demonstrated to have a favourable safety and efficacy profile when compared with HyateC and can be a valuable treatment option for control of bleeding in AHA patients.

Keywords: acquired haemophilia A, bypass agents, FVIII, FVIII inhibitors, Obizur, recombinant porcine FVIII
Prophylaxis with by-passing agents

- aPCC infused prophylactically at a target dose of 85 U/kg on 3 nonconsecutive days per week
- 62% reduction in all bleeding episodes
- 61% reduction in hemarthroses
- 72% reduction in target-joint bleeding (≥3 hemarthroses in a single joint during a 6-month treatment period)
To evaluate whether secondary prophylaxis with rFVIIa can safely and effectively reduce bleeding frequency as compared with conventional on-demand therapy

- rFVIIa infused at a dose of 90 or 270 µg/kg per day
- Bleeding frequency was reduced by 45% and 59% during prophylaxis with 90 and 270 µg/kg, respectively
- However, there was no difference detected between doses
Immune Tolerance Induction (ITI)

- First reported in the late 1970s in Germany
- Consists of regular administration of FVIII in order to render the immune system tolerant to the antigen
- Successful ITI is able to normalize FVIII pharmacokinetics and improve the patients’ quality of life
- Success rates vary from approximately 60 to 80% depending on the protocol used

(Gomez K et al Blood Transf 2014; 12 (Suppl 1):s319-29)
Protocol regimens

• There are different dosing regimens to achieve immuno tolerance

• The Bonn protocol was the first
  - High-doses FVIII 100-150 IU/Kg body weight twice a day

• The Dutch protocol
  - 25-50 IU/Kg body weight three times a week

• The German guidelines (Deutsche Arztekammer 2008)
  - 50-100 IU/Kg body weight three times a week for ITI with low titer inhibitor
  - 100-200 IU/Kg body weight twice a day for ITI with high titer inhibitor

What is the appropriate regimen?

• No standard ITI regimen exists

• 2012 - the first prospective randomized trial of ITI in patients with severe hemophilia A with high titer inhibitors

The principal results of the International Immune Tolerance Study: a randomized dose comparison

Charles R. M. Hay¹ and Donna M. DiMichele,² on behalf of the International Immune Tolerance Study

(Blood. 2012; 119(6):1335-1344)
What is the appropriate regimen?

Aim: low dose regimen (50 IU/Kg 3 times/week) vs a high dose regimen (200 IU/Kg/day)

- The success rate was rather high and similar in the two arms (70%)
- The time taken to achieve a negative titer were shorter with the high dose than low dose regimen
- Patients treated with the low dose bled significantly more than the those in high dose arm

(Hay C et al, Blood 2012;119:1335-1344)
ITI with plasma-derived with VWF

- ITI treatment with high-purity FVIII resulted in a lower success rate (29%) than with concentrates containing von Willebrand Factor (91%)

- May the type of FVIII product predict ITI outcome?

(Auerswald G et al. Haematologica 2003; 88: EREP05)
Primary and rescue immune tolerance induction in children and adults: a multicentre international study with a VWF-containing plasma-derived FVIII concentrate


Haemophilia (2014), 20, 83–91

Treatment with a single pdFVIII/VWF concentrate results in a high ITI success rate

First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study

W. Kreuz, C. Escuriola Ettingshausen, V. Vdovin, N. Zozulya

On behalf of the OBSITI study group and the OBSITI committee

Haemophilia (2016), 22, 87–95

<table>
<thead>
<tr>
<th>ITI regimen</th>
<th>Children</th>
<th>Adults</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Complete success</td>
<td>Partial success</td>
<td>Failure</td>
</tr>
<tr>
<td>Primary</td>
<td>21 (65.6)</td>
<td>7 (21.9)</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td></td>
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</tbody>
</table>

Values within parenthesis are expressed in percentage.
Management of patients who failed ITI

- Approximately 20-30% of patients fail ITI
  - Increasing doses up to 200 IU/Kg
  - Switching to a plasma derived FVIII containing VWF
  - Immune suppressive drugs, e.g. rituximab

(Gomez K et al Blood Transf 2014; 12 (Suppl 1):s319-29)
Rituximab and immune tolerance- UK study

- 15 patients at seven centers were treated with rituximab as part of an immune tolerance regimen
- Rituximab at a dose of 375 mg m\(^{-2}\) once a week for four consecutive weeks
- 12 patients received FVIII, 10 were treated with at least 200 IU/kg/day, one received 100 IU/kg/day and one was treated with 100 IU/kg/day three times a week
- Six patients (50\%) achieved a negative inhibitor titer and seven (58\%) had a clinically beneficial response

• 16 patients were treated with rituximab only at a dose of 375 mg m\(^{-2}\) once a week for four consecutive weeks.

• This led to lower inhibitor levels, but its effect as a solo treatment strategy was modest.

• Future studies are indicated to determine the role of rituximab as an adjunctive therapy in immune tolerisation strategies.
New treatment options

• Novel bypassing agents are under development to improve shortcomings of currently available inhibitor therapies

• The aims are to produce novel drugs that
  – have a longer half-life
  – less thrombogenic
## New treatment options

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
<th>Mechanism of prolonged half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albumin fusion</strong></td>
<td>Fusion of the Fc domain of albumin to protein.</td>
<td>Binding of albumin to FcRn delays lysosomal degradation of the fusion protein and recycles it back into the circulation.</td>
</tr>
<tr>
<td><strong>Carboxyl terminal peptide (CTP)</strong></td>
<td>Fusion of the C terminus peptide of human chorionic gonadotropin (hCG) to target protein.</td>
<td>Improves the half-life of therapeutic proteins and maintains their biological activity.</td>
</tr>
<tr>
<td><strong>Aptamer</strong></td>
<td>Single-stranded oligonucleotides.</td>
<td>Binds with high affinity and specificity to their targets, inhibiting disease processes.</td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>Monoclonal antibody and humanized bispecific antibody.</td>
<td>Binds with high affinity and specificity to the target molecule, abolishing the activity.</td>
</tr>
<tr>
<td><strong>RNA interference (RNAi)</strong></td>
<td>Small interference RNA (siRNA), fundamental cellular pathway of gene silencing.</td>
<td>RNAi therapeutics offer the potential to potently and specifically reduce the expression of disease-causing genes.</td>
</tr>
</tbody>
</table>
Anti-TFPI antibody
*(concizumab)*

- **TFPI** consists of three Kunitz-type protease inhibitor domains

- **TFPI** has a double inhibitory effect:
  - inactivates factor Xa (FXa)
  - prevents FX activation by binding the tissue factor (TF) – factor VIIa (FVIIa)

- A humanized monoclonal antibody against TFPI (concizumab) has a high affinity for the K2 domain of TFPI

- By preventing FXa binding to TFPI, concizumab also prevents TFPI inhibition of TF–FVIIa complex, thereby abrogating TFPI function, resulting in enhanced FXa and thrombin generation in vitro
RNA Interference (RNAi)
A New Class of Innovative Medicines

- is a cellular pathway of gene silencing in a sequence-specific manner at the mRNA level that occurs in organisms ranging from plants to mammals

- a short interfering RNA (siRNA), ALN-AT3, employing a hepatocyte targeting ligand has been developed against antithrombin (AT)
A subcutaneous administered investigational RNAi therapeutic (ALN-AT3) targeting antithrombin for treatment of hemophilia: Interim weekly and monthly dosing results in patients with hemophilia A and B

(Pasi K et al. 57th ASH Annual Meeting)

Analysis of thrombin generation by AT lowering quartiles
A subcutaneous administered investigational RNAi therapeutic (ALN-AT3) targeting antithrombin for treatment of hemophilia: Interim weekly and monthly dosing results in patients with hemophilia A and B

(Pasi K et al. 57th ASH Annual Meeting)

Peak thrombin achieved post AL-AT3 dose compared to peak thrombin achieved with FVIII

Achieved peak thrombin generation values equivalent to >40% FVIII
ACE910 bispecific antibody

- a humanized bispecific antibody to factor IXa (FIXa) and factor X (FX), termed ACE910/ hBS23

- **ACE910** binds FIXa with one arm and FX with the other placing in spatially appropriate positions, as FVIIIa does, and promote FIXa-catalyzed FX activation.
ACE910 bispecific antibody

Phase I- II Results

- Patients with severe hemophilia A (FVIII:C <1%, ages 12 to 58 years; with and without inhibitors) treated with one-weekly subcutaneous injection of ACE910 at dose levels 0.3, 1 and 3mg/kg

**Efficacy**
- Once-weekly subcutaneous ACE910 prophylaxis has a promising efficacy profiles in severe hemophilia A patients including patients with FVIII inhibitors

**Safety**
- All adverse events of mild or moderate intensity
- No adverse events related to hypercoagulation
- Anti-ACE910 antibodies, which did not affect ACE910 pharmacokinetics and pharmacodynamics, were developed in three patients

# New treatment options

<table>
<thead>
<tr>
<th>Technology</th>
<th>Product</th>
<th>Half-life</th>
<th>Somministration</th>
<th>Status</th>
<th>Patients Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFVIIa</td>
<td>Albumin fusion</td>
<td>rFVIIa-FP</td>
<td>8.5 hours</td>
<td>Intravenous</td>
<td>Phase II/III (NCT02484638) Ongoing</td>
</tr>
<tr>
<td></td>
<td>Fusion of the C terminus peptide (CTP)</td>
<td>rFVIIa-CTP</td>
<td>NA</td>
<td>Intravenous and subcutaneous injection</td>
<td>Phase I/IIa NCT02418793 Ongoing</td>
</tr>
<tr>
<td>Inhibition of natural anticoagulants</td>
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<tr>
<td>anti-TFPI Antibody</td>
<td>Concizumab (mAb2021)</td>
<td>once weekly</td>
<td>Subcutaneous injections</td>
<td>Phase I (NCT02490787) Ongoing</td>
<td>Haemophilia A (21) and B (3) patients</td>
</tr>
<tr>
<td>RNA interference (RNAi) against AT</td>
<td>ALN-AT3</td>
<td>once weekly</td>
<td>Subcutaneous injections</td>
<td>Phase I/II Ongoing (NCT02554773)</td>
<td>Haemophilia A (12) and B (2) patients</td>
</tr>
<tr>
<td>Promotion of thrombin generation by mimicking the cofactor activity of FVIII</td>
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</tr>
<tr>
<td>Bispecific antibody to FIXa/FX</td>
<td>ACE910</td>
<td>once weekly</td>
<td>Subcutaneous injections</td>
<td>Phase I/II completed</td>
<td>Haemophilia A patients (7), Hemophilia patients with inhibitor (11)</td>
</tr>
</tbody>
</table>
Conclusion

• Inhibitor development is the major complication of hemophilia therapy

• Inhibitor eradication is the only way to significantly impact the morbidity related to this complication

• The development of novel therapies should lead to increased therapeutic options with improved efficacy for hemophilia patients with inhibitor

• Cost should remain affordable