Inhibitors, EIN and inhibitor treatment guidelines

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European Haemophilia Consortium / World Haemophilia Day
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EDQM
Strasbourg, France
Positive and negative impact of substitution with FVIII in a patient with severe HA

- **Haemostatic Efficacy**
  - Bleeding: control/prevention

- **Inhibitor formation**
  - Formation of antibodies to FVIII

- **Infectious complications**
  - Pathogen transmission

- **Adverse Events**
  - Adverse events (AEs)

**Safety**
## Current ambitions in haemophilia therapy

<table>
<thead>
<tr>
<th>Goals</th>
<th>In clinical practice</th>
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<tbody>
<tr>
<td>« Zero » bleed</td>
<td>Achievable with personalized primary or secondary prophylaxis</td>
</tr>
<tr>
<td>« Zero » infection</td>
<td>Achievable with current plasma-derived or recombinant concentrates</td>
</tr>
<tr>
<td></td>
<td>Eradication of HCV now possible in most patients</td>
</tr>
<tr>
<td>« Zero » Inhibitor</td>
<td>Currently impossible to avoid INH formation in many patients</td>
</tr>
<tr>
<td></td>
<td>Currently impossible to eradicate INH in many patients</td>
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</table>
The current reduction in infective risk of fractionated plasma products has been achieved through a multi-step process.

No transmission of HBV, HCV or HIV attributable to manufactured plasma derivatives licensed for use in the US has been reported since 1985.

The most modern recombinant products do not contain exogenous animal or human components and therefore do not carry a risk of transmission of known or unknown pathogens.
Not all previously untreated patients (PUPs) with severe HA are tolerant to exogenous FVIII

70-95% of the patients do not develop an INH

Ignorance of therapeutic FVIII?
Induction of tolerance?

5-30% of previously untreated patients receiving FVIII develop an INH

FVIII inhibitors
The worst complication that commonly occurs to PUPS with severe hemophilia

(30-40%) Inhibitor development
Development of an inhibitor is devastating – it results in ...

Need for ports
Need for ITI
More difficult to treat bleeds
↑ susceptibility to life-threatening bleeds
Worse quality of life
The poor long-term outcome in patients with persistent inhibitor compared with haemophilia without inhibitors ....

Leissinger et al, Blood 2001

Morfino et al, Haemophilia, 13:606-12 2007
Impact of inhibitors on hemophilia A mortality in the US

- Retrospective analysis (CDC) – 7386 patients with severe HA
- 627 patients with active inhibitors
- Active inhibitor patients more likely among young (<11yrs) and older age group (>45 yrs)
- Intracranial hemorrhage was the major cause of death among inhibitor (70%) and non-inhibitor (67%) patients

- *Haemophilia related (bleeding events) cause of death was significantly more frequent among patients with active inhibitors (42%) than among those without (12%) (p<0.0001)*

Walsh et al, AJH 2015
Improvement in immunological safety has been less successful than infectious safety

Many risk factors for INH development have been identified and studied

Strategies to bypass FVIII / FIX and eradicate INH have been successfully developed and validated

Strategies have been proposed to estimate, reduce or minimize the risk of INH development

For many PUPS with severe HA, INH development remains a fatality
INHIBITOR in patients with haemophilia: short history of diagnosis, risk factors and treatment strategies


Successful treatment of hemophilia a inhibitor patients with an induced immunotolerance

Cohort studies
- Bonn protocol
- Malmö protocol
- Dutch protocol
- Low/intermediate dose protocols

National and International Registries
- IITR
- NAITR
- GITR

Randomized trials
RISK FACTORS FOR INHIBITOR DEVELOPMENT

**Non-modifiable**
- Haemophilia severity
- FVIII/IX mutations
- HLA Class II

**Modifiable**
- Intensive FVIII/IX exposure
- Immunological challenge

**Type of treatment**
- Type of FVIII/IX concentrate
- Therapeutic regimen

**Genetics**
- Polymorphisms in immunoregulatory genes
- Family history
- Ethnicity

**FVIII/FIX ANTIBodies**

**Treatment-related**
- Intensive FVIII/IX exposure
- Immunological challenge
## Inhibitor risk factors in previously untreated patients

<table>
<thead>
<tr>
<th>Inhibitor risk factor</th>
<th>Level of evidence</th>
</tr>
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<tbody>
<tr>
<td>Family history</td>
<td>Well established</td>
</tr>
<tr>
<td>Race</td>
<td>Established but not well understood</td>
</tr>
<tr>
<td>F8 mutation type</td>
<td>Well established</td>
</tr>
<tr>
<td>F8 polymorphisms</td>
<td>Conflicting reports</td>
</tr>
<tr>
<td>MHC classes I/II</td>
<td>Conflicting reports</td>
</tr>
<tr>
<td>Polymorphisms in cytokines and inflammatory genes</td>
<td>Some evidence but not well understood</td>
</tr>
<tr>
<td>Trauma/surgery</td>
<td>Established but not well understood</td>
</tr>
<tr>
<td>Inflammation/infection</td>
<td>Established but not well understood</td>
</tr>
<tr>
<td>Early intense exposure</td>
<td>Established but not well understood</td>
</tr>
<tr>
<td>Age at first exposure</td>
<td>No clear evidence</td>
</tr>
<tr>
<td>Early Prophylaxis</td>
<td>Some evidence but not well understood</td>
</tr>
<tr>
<td>Vaccinations</td>
<td>No clear evidence</td>
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Adapted from Carcao M. and Ewenstein B. Haemophilia, Volume 22, Issue 1 January 2016 Pages 22–31
RISK FACTORS FOR INHIBITOR DEVELOPMENT

- Haemophilia severity
- FVIII/IX mutations
- HLA Class II

Genetics

- Polymorphisms in immunoregulatory genes
- Family history
- Ethnicity

Treatment-related

- Intensive FVIII/IX exposure
- Immunological challenge

Avoid danger signals and antigen load

Type of treatment

- Type of FVIII/IX concentrate
- Therapeutic regimen
INHIBITOR: TREATMENT STRATEGIES

- **Inhibitor**
  - **Bleed Management** → **Prevent/Stop the Bleeding**
  - **Long-term Strategy** → **Eradicate Inhibitor** → **Long-term prophylaxis with deficient clotting factor**
Current Treatment Options for Inhibitors

Three approaches:

1. Eradicate the inhibitor permanently through ITI
2. Treat acute bleeds with bypassing agents
3. Prophylaxis with by-passing agents

Treatment strategies in inhibitor patients

Table 5. Preliminary results from the decision analytic model, estimated over the lifetime of the patient. Costs are in 2013 US dollars; discounting is at 3%.

<table>
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<tr>
<th>ITI</th>
<th>On-demand</th>
<th>Prophylaxis</th>
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<tr>
<td>Drug and hospitalization cost (discounted)</td>
<td>$22,201,832</td>
<td>$38,656,756</td>
</tr>
<tr>
<td>Life years (projected)</td>
<td>74.3</td>
<td>69.6</td>
</tr>
<tr>
<td>QALYs (discounted)</td>
<td>25.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Bleeding events (projected)</td>
<td>891</td>
<td>1819</td>
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ITI, immune tolerance induction; QALYs, quality-adjusted life years.


**ITI associated with**
- lower drug and hospitalization costs
- longer projected life expectancy
- Higher QALY's
- Fewer projected bleeding events

compared to prophylaxis or on demand therapy with BPA
Treatment strategies in inhibitor patients who failed ITI / not eligible for ITI

- Patients with Persistent inhibitors
  - On demand therapy with BPA
    - High costs
    - ↑ Arthropathy
    - ↓ QoL
  - Prophylaxis with BPA
    - High costs
    - Preservation of joint status
    - Maintain QoL
Cumulative Costs Over Time for Patients Treated via ITI, Prophylaxis, and On-demand Treatment with BPA
Patients with INH: An heterogeneous population

Three groups

- Patients with a recently diagnosed INH (Low or High Titre) candidates for ITI
- Patients who underwent successful eradication
- Patients with long-standing or persistent INH ITI failure or never treated with ITI  How many?
Immune tolerance induction (ITI)

• Immune tolerance induction (ITI) is the only therapeutic approach proven to eradicate persistent inhibitors in haemophilic patients, thus allowing one to restore safe and effective FVIII replacement treatment and, particularly, the feasibility of prophylaxis.

• This objective is crucial in children with inhibitors to preserve their joints from haemophilic arthropathy, to provide a satisfactory quality of life, and to reduce long-term morbidity and mortality and the impact of inhibitor-related complications on healthcare costs.
ITI : A long-term fruitful investment

The huge economic investment of ITI may provide long-term FVIII tolerance and consequent benefits in the large majority of patients.
The many current challenges that INH patients and treaters are facing daily:

- Difficult diagnosis
- Complex management (choice of optimal treatment modalities, cost of ITI, venous access, need for highly specific multidisciplinary care...)
- Major need for patients’ active involvement / commitment
- Patients’ isolation, under-representation
- Limited scientific evidence / lack of valid data
- Lack of ambition / perceived as an unobvadable fatality
# Ambitions in haemophilia care

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How can we realistically and practically achieve this?
The 10 European Principles of Hemophilia Care

1. A central hemophilia organisation with supporting local groups
2. National hemophilia patient registries
3. Comprehensive care centres and hemophilia treatment centres
4. Partnership in the delivery of hemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis treatment
8. Specialist services and emergency care
9. Management of inhibitors
10. Education and research

Principle 9

**Management of Inhibitors**

- Some people with haemophilia develop “inhibitors”, when their bodies inactivate the replacement clotting factor treatment. Those affected need to have immediate access to optimum treatments.

- Where appropriate, immune therapy induction therapy (ITT) and the management of bleeding should be administered by clinicians with the necessary expertise, in hospitals with appropriate clinical and laboratory resources.
Recommendation 7: People with inhibitors should have access to immune tolerance.

• With immune tolerance induction, 70% of patients achieve complete tolerance and a further 5% achieve a partial response.

• ITI is cost effective in the long term through the avoidance of repeated treatment of bleeding episodes with much more expensive bypassing agents.

• Immune tolerance induction therapy is still not readily available in several European countries.

Hay CR & DiMichele DM. Blood 2012; 119: 1335-44
Surgery in patients with haemophilia and inhibitors can be performed safely using bypassing agents.

Many patients with inhibitors are denied elective surgery which such as arthroplasty which could improve their quality of life.

Some treatment centres still have reservations about the potential for bleeding. The initial high cost may be a considerable barrier. A number of economic evaluations indicate that surgery may prove cost effective in the longer term.

Surgery in patients with inhibitors should only be carried out in centres with previous experience. Where this is not feasible locally, patients should be referred to another centre with the requisite experience (across national borders if necessary).

Kreuth IV: European consensus proposals for treatment of haemophilia with coagulation factor concentrates

People with inhibitors should have access to elective surgery at a specialist centre with relevant experience

- Surgery in patients with haemophilia and inhibitors can be performed safely using bypassing agents.

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Establishment of European principles of inhibitor treatment (EHC – EAHAD)

1. Lifelong Awareness of the Incidence of Inhibitors and Risk Factors
2. Early Recognition and accurate diagnosis
3. Organisation of Care and Communication Between All Stakeholders
4. Inhibitor eradication by Immune Tolerance Induction Therapy
5. Hemostatic Treatment with Bypassing Agents
6. Access to and Optimal Preparation for Surgery and Invasive Procedures
7. Delivery of Specialist Nursing Care
8. Provision of Tailored Physiotherapy Care
9. Access to Psychosocial Support
10. Involvement in the Research and Innovation
EIN
European Inhibitor Network
WORLD HAEMOPHILIA DAY
Strasbourg, 19 April 2017
THANK YOU FOR YOUR ATTENTION