ITI today and tomorrow

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<table>
<thead>
<tr>
<th>Category</th>
<th>Entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
<td>No conflict of interest to disclose</td>
</tr>
<tr>
<td>Research support/PI</td>
<td>Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Roche, Shire</td>
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<tr>
<td>Scientific advisory board</td>
<td>Biotest, CSL Behring, Novo Nordisk, Octapharma, Shire</td>
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<tr>
<td>Major stockholder</td>
<td>No conflict of interest to disclose</td>
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<td>Patents</td>
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<td>Honoraria/Consultancy</td>
<td>Biotest, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Shire</td>
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<tr>
<td>Travel support</td>
<td>Bayer, Biotest, CSL Behring, Grifols, Octapharma, Shire</td>
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<tr>
<td>Other</td>
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INHIBITOR DEVELOPMENT IN SEVERE HAEMOPHILIA A – A TYPICAL CASE

- Patient with severe haemophilia A and intracranial bleed as the first manifestation of the disease
- Intron-22-inversion
- Inhibitor developed after intensive treatment with pdFVIII after 5 ED at 11 months of age
- Historical peak titre 217 BU/ml – current inhibitor titer 68 BU/ml
- Patient with poor prognosis for ITI (inhibitor titer >10 BU/ml at start of ITI, historical inhibitor titer >200 BU/ml)

**Current treatment options**

- On-demand treatment with BPA
- Prophylaxis with BPA or emicizumab
- ITI
# ITI PROTOCOLS IN HAEMOPHILIA A

<table>
<thead>
<tr>
<th>Protocol Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonn protocol/ high dose protocol¹</td>
<td>100-150 IU FVIII/kg BW every 12 hours; according to the bleeding tendency concomitant treatment with FEIBA 50 U/kg or rFVIIa twice daily</td>
</tr>
<tr>
<td>High dose protocol</td>
<td>200 IU FVIII/kg every 24 hours</td>
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<tr>
<td>Intermediate dose protocol</td>
<td>100 IU FVIII/kg daily</td>
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<tr>
<td>van Creveld protocol/ low dose protocol²</td>
<td>25(-50) IU FVIII/kg every other day</td>
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<tr>
<td>Malmö protocol³</td>
<td>Extracorporeal immune adsorption with Protein-A-columns on 2 consecutive days, immunosuppression (cyclophosphamide), immunomodulation (IVIG), administration of FVIII concentrate at 8-12 hour intervals</td>
</tr>
<tr>
<td>Protocols including immunosuppressives⁴</td>
<td>Rituximab, MMF, dexamethason, IVIG, FVIII resp. FIX in haemophilia B</td>
</tr>
</tbody>
</table>

INDIVIDUALIZING ITI FOR THE PATIENT

Individualization of ITI – maximizing success

- Candidates for ITI?
- Which ITI strategy/protocol/dosage in whom?
- Changing dosage/protocol during ITI?
- Which product type for ITI? Switching product types during ITI?
- Prophylaxis during ITI?
### MAJOR DRIVER FOR PERSONALIZATION OF ITI – PREDICTORS OF GOOD AND BAD OUTCOME OF FIRST ITI

<table>
<thead>
<tr>
<th>Good risk</th>
<th>Bad risk</th>
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<tbody>
<tr>
<td>Pre ITI titre &lt;10 BU/ml</td>
<td>Pre ITI titre &gt;10 BU/ml</td>
</tr>
<tr>
<td>Historical peak titre &lt;200 BU/ml</td>
<td>Historical peak titre &gt;200 BU/ml</td>
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<tr>
<td>Peak on ITI &lt;100 BU/ml</td>
<td>Peak on ITI &gt;100 BU/ml</td>
</tr>
<tr>
<td>Time inhibitor dx to start ITI &lt;5 yrs</td>
<td>Time inhibitor dx to start ITI &gt;5 yrs</td>
</tr>
<tr>
<td>Low age?</td>
<td>High age?</td>
</tr>
<tr>
<td>No interruption of ITI</td>
<td>Interruption &gt;2 weeks of ITI</td>
</tr>
</tbody>
</table>

BU, Bethesda Units; ITI, immune tolerance induction

- Patients with earlier first-line ITI failure – bad risk (poor prognosis)
**Candidates for ITI** – Define candidates for ITI (primary/secondary)

**Start of ITI** – Immediate start regardless of inhibitor titre vs postpone ITI until inhibitor titre is <10 BU/ml

**Choice of factor replacement agent for first-line/second-line ITI** – Product used at inhibitor development for first-line ITI; preference to use VWF-FVIII or FVIIIFc for rescue ITI

**Dosage/protocol** – Intermediate or high dose preferred for rapid BU negativation and bleed prevention in good prognosis patients (dosing can be adapted to ITI course); in poor prognosis patients high dose regimens preferred; alternative protocols including emicizumab

**Prophylaxis during ITI** – Prevention of bleeds in the bleeding ITI patient (BPA and potentially emicizumab)

**Protocols including immunosuppressive therapy** – Rituximab and FVIII concentrate combined with other immunosuppressive agents
ITI with pdVWF-FVIII 2.5 weeks after inhibitor detection, according to the Bonn protocol: FVIII 100 IU/kg 2x/day + aPCC prophylaxis until inhibitor 1 BU

- Negative inhibitor after 2.8 months
- Normal FVIII recovery after 6.1 months
- Normal FVIII t\(_{1/2}\) after 9.8 months
- No bleeds during ITI
- No relapse of inhibitor during prophylaxis with pdFVIII-VWF since 8.4 yrs

**Case report**

<table>
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<tr>
<th>Start of ITI</th>
<th>Negative BU 2.8 mo</th>
<th>Normal FVIII recovery 6.1 mo</th>
<th>Normal FVIII t(_{1/2}) 9.8 mo</th>
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ITI STRATEGIES – VARIABLES TO PERSONALIZE ITI REGIMEN IN SEVERE HA

- Switch to VWF-FVIII concentrate (100 IU/kg twice daily i.v.) or rFVIIIIFc if ITI fails
TODAY´S ITI PROTOCOLS ARE SAFE AND EFFECTIVE

- ITI – 60-90% successful eradication of inhibitors
- Success 69.7% (Int. ITI study comparing LD and HD ITI in good prognosis patients)\(^1\)
- No safety concerns – 38 study related SAE´s in the Int. ITI-study (35 catheter-related, 1 FVIII reaction, 1 trauma)
- Duration of ITI

<table>
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<tr>
<th></th>
<th>Van Creveld protocol (low dose)(^2)</th>
<th>Bonn protocol(^3) (high dose /2x/d)</th>
<th>Malmö protocol(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment (median, range)</td>
<td>&lt;40 BU 6 mo (1-9)</td>
<td>4 mo (0.5-42)</td>
<td>9-37 days</td>
</tr>
<tr>
<td></td>
<td>&gt;40 BU 19 mo (12-27)</td>
<td></td>
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- Low relapse rate (16% Int. ITI study – 0% Obs. ITI)

REASONS NOT TO PERFORM ITI IN THE ERA OF EMICIZUMAB

- ITI – too burdensome treatment for the child and his family
- Need for central venous access (surgery)
- Prophylaxis with emicizumab is highly effective and less burdensome
- ITI is not very effective in high titre inhibitors (60-90% but intention-to-treat-analysis of the international ITI study revealed much lower success rate app. 40%)
- High costs
- How many patients maintain long-term immune tolerance?

REASONS TO PERFORM ITI IN THE ERA OF EMICIZUMAB

- Difficulties to control bleeds in inhibitor patients
- Incidence of break-through bleeds – around 40% of patients treated with emicizumab develop bleeds which have to be treated

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Arm B: NO previous BPA prophy</th>
<th>Arm A: 1.5 mg/kg emicizumab weekly</th>
<th>Arm C\textsubscript{NIS}: Previous BPA prophy</th>
<th>Arm C: 1.5 mg/kg emicizumab weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=18</td>
<td>N=35</td>
<td>N=24</td>
<td>N=24</td>
</tr>
<tr>
<td>Treated bleeds**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR (95% CI)</td>
<td>23.3 (12.33; 43.89)</td>
<td>2.9 (1.69; 5.02)</td>
<td>15.7 (11.08; 22.29)</td>
<td>3.3 (1.33; 8.08)</td>
</tr>
<tr>
<td>% reduction (RR), p-value</td>
<td>87% (0.13), &lt;0.0001</td>
<td></td>
<td>79% (0.21), 0.0003</td>
<td></td>
</tr>
<tr>
<td>% patients with 0 bleeds (95% CI)</td>
<td>5.6 (0.1; 27.3)</td>
<td>62.9 (44.9; 78.5)</td>
<td>12.5 (2.7; 32.4)</td>
<td>70.8 (48.9; 87.4)</td>
</tr>
</tbody>
</table>

All bleeds (treat /not treated)

|          |                                 |                                   |                                |                               |
| ABR (95% CI)     | 28.3 (16.79; 47.76)           | 5.5 (3.58; 8.60)                  |                                |                               |
| % reduction (RR), p-value | 80% (0.20), <0.0001         |                                   |                                |                               |
| % patients with 0 bleeds (95% CI) | 5.6 (0.1; 27.3)            | 37.1 (21.5; 55.1)                 |                                |                               |

Treated joint bleeds

|          |                                 |                                   |                                |                               |
| ABR (95% CI)     | 6.7 (1.99; 22.42)            | 0.8 (0.26; 2.20)                  |                                |                               |
| % reduction (RR), p-value | 89% (0.11), 0.0050         |                                   |                                |                               |
| % patients with 0 target joint bleeds (95% CI) | 50.0 (26.0; 74.0)         | 85.7 (69.7; 95.2)                 |                                |                               |

**Treated bleeds defined as bleeds directly followed by haemophilia medication reported to be for ‘treatment of a bleed’, without an intervening bleed and irrespective of the time between treatment and the preceding bleed

REASONS TO PERFORM ITI IN THE ERA OF EMICIZUMAB

- Higher bleed-related mortality in inhibitor patients compared to non-inhibitor patients
- Retrospective analysis from the UDC surveillance project of US Centers for Disease Control (CDC) – 7386 patients with severe HA
- 627 patients with active inhibitors
- Active inhibitor patients more likely among young (<11 yrs) and older age group (>45 yrs)
- 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)

FENOC STUDY – DISCORDANT RESPONSE TO BPA IN THE SETTING OF BLEEDS

- Prospective, head-to-head, randomized, crossover, open-label study to assess safety and hemostatic efficacy/equivalence of FEIBA therapy and rFVIIa* 6 hours after treatment of bleeding episode

*Typical treatment initiated within 4 hours of bleed onset.

**REASONS TO PERFORM ITI IN THE ERA OF EMICIZUMAB**

- **Safety** – treatment of bleeds with BPA in the presence of emicizumab – high risk of thrombotic complications

- 111 inhibitor patients treated with emicizumab
  - 37 patients treated with rFVIIa
    - 140 treatment episodes
    - No TMA/TE with emicizumab + rFVIIa treatment alone
  - 20 patients treated with aPCC
  - 78 treatment episodes

- ≤100 U/kg/day
  - 52 treatment episodes
    - No TMA or TE
  - ≥24 hours
    - 5 treatment episodes
      - No TMA or TE

- >100 U/kg/day
  - 13 treatment episodes
    - No TMA or TE
  - ≥24 hours
    - 8 treatment episodes
      - 5 events of TMA/thrombosis*

- 5/8 patients receiving >100 U aPCC for >24 hrs developed thrombosis or TMA
- TMA has never been observed over decades of treatment with BPA

*Two patients also received rFVIIa prior to/during the event. TE, thromboembolism.  Updated data cutoff – April 21, 2017, including 8 additional patients.
## Emicizumab and FVIII – mode of action

![Diagram showing modes of action of FVIIIa and ACE910/Emicizumab](image)

<table>
<thead>
<tr>
<th>Multiple sites of interaction</th>
<th>Single sites of interaction</th>
</tr>
</thead>
</table>
| High affinity for enzyme & substrate  
  (low to high nanomolar range) | Low affinity for enzyme & substrate  
  (micromolar range) |
| Specific for FIXa and FX  
  (no binding to FIX and FXa) | No distinction between zymogen and enzyme  
  (FIX vs FIXa and FX vs FXa) |
| Full cofactor activity  
  - promotes phospholipid binding  
  - stabilizes FIXa active site  
  - bridges FIXa to FX | Partial cofactor activity  
  - bridges FIXa to FX |
| Enzyme and substrate are in excess over cofactor | Antibody is in excess over enzyme and substrate |
| FVIIIa has on/off mechanism | Emicizumab has no on/off mechanism |
| High level of self-regulation | Low level of self-regulation |

Lenting et al. Blood 2017;130:2463-8
REASONS TO PERFORM ITI IN THE ERA OF EMICIZUMAB

• Safety/deaths – unresponsive bleeds/bleeds with fatal outcome

CASE 1 [Compassionate Use]¹,³
- 38 y male
- Emi start: Sept 2015
- 17 Feb 2016: pulmonary infarction + Sepsis → ICU
- 21 Feb 2016: ICH → epptacog alfa for ventriculotomy
- Allergic reaction to FEIBA & susoctocog alfa
- DEATH: ICH [24 Feb 2016]
- HCP assessment: unrelated to emicizumab
- Autopsy: ICH + Septic emboli [not DVT or thrombotic emboli]

CASE 2 [HAVEN 1]¹
- 41 y white male
- Co-morbidities: perforated bowel surgery, VHC+, arterial HT
- Emicizumab start: 8 Jun 2016
- 13 bleeds during the study that were not treated with BPA
- 30 Jan 2017: rectal bleed
- 30 Jan to 2 Feb: epptacog alfa → 11 doses over 3 consecutive days → No response to epptacog alfa
- 2 Feb to 5 Feb: FEIBA for 4 days → Bleed stopped temporarily
- 5 Feb 2017: TMA → FEIBA stopped and plasma exchange and albumin started
- DEATH: rectal bleed [8 Feb 2017]
- HCP assessment: unrelated to emicizumab

CASE 3 [Compassionate Use]²,³
- Age: unk → USA
- Co-morbidities: multiple ICH in the past due to predisposing factors
- DEATH: ICH in 2017
- HCP assessment: unrelated to emicizumab

CASE 4 [Compassionate Use]²,³
- Age: adult
- Co-morbidities: abdominal pseudo-tumor
- DEATH because of complications related to this pre-existing condition
- HCP assessment: unrelated to emicizumab

CASE 5 [Compassionate Use]²,³
- Age: unk → USA
- Co-morbidities: UNK
- Bleeding after aorta coarctation repair: elective major vascular surgery
- Tx with susoctocog alfa and FEIBA without response
- DEATH because of bleed in 2018
- HCP assessment: unrelated to emicizumab

CASE 6 [STASEY]
- Age: unk
- Co-morbidities: unk
- DEATH because of severe head trauma
- HCP assessment: unrelated to emicizumab

REASONS TO PERFORM ITI IN THE ERA OF EMICIZUMAB

- Management of major surgery
- Potential need of FVIII for non-haemostatic functions (e.g. bone health, control of inflammation, prevention of hypertension etc.)
- No access to gene therapy with existing FVIII inhibitors
- ADAs
ITI in the future
ALTERNATIVE ITI STRATEGIES COMBINING EMICIZUMAB AND FVIII FOR ITI MIGHT …

- Reduce invasiveness of prophylaxis during ITI, by once weekly s.c. administration of emicizumab
- Provide haemostasis in inhibitor patients during (low-dose) ITI and prevent break-through bleeds
- Lead to modification of ITI strategies (e.g. start of ITI) and ITI treatment protocols (e.g. less frequent ITI administrations)
There are no data on the use of emicizumab prophylaxis to prevent bleeding episodes during immune tolerance induction (ITI), and the safety of emicizumab in this situation is unproven. Emicizumab should only be considered during ITI for patients with significant and frequent breakthrough bleeds. The dose of FVIII should be tailored to avoid high FVIII levels which will occur as FVIII tolerance is approach
ITI STRATEGIES INCLUDING EMICIZUMAB FOR PROPHYLAXIS IN HR INHIBITORS

ITI combined with prophylactic administration of emicizumab

- LD protocol (25-50 IU FVIII/kg 3 x weekly) + emicizumab once weekly s.c.
- Atlanta protocol (100 IU rFVIII or EHL-FVIIIIFc/kg 2-3 x weekly) + emicizumab once weekly s.c.
- Bonn protocol (200 IU FVIII/kg 1 x/d) + emicizumab once weekly s.c.
A CHILD WITH HIGH TITER INHIBITOR – 3 YEARS – ON ITI

- Development of high titer inhibitor at the age of 1.4 yrs after 20 ED (7.5 BU/ml) during prophylaxis with rFVIII
- Large deletion spanning Exon 1-14
- Start of ITI according to the Bonn protocol 100 IU rFVIII/kg twice daily
- aPCC 50 U/kg twice daily added to ITI
- Switch to VWF-FVIII
- Dose increase to 150 IU FVIII/kg twice daily
- During ITI course multiple severe bleeds requiring hospitalisation and blood transfusion

<table>
<thead>
<tr>
<th>Time [months]</th>
<th>Inhibitor titre [BU/ml]</th>
</tr>
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<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5.0</td>
<td>50.0</td>
</tr>
<tr>
<td>10.0</td>
<td>100.0</td>
</tr>
<tr>
<td>15.0</td>
<td>150.0</td>
</tr>
<tr>
<td>20.0</td>
<td>200.0</td>
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- Emicizumab once weekly combined with FVIII 40 IU/kg 3 times weekly
- No bleeds – decrease of inhibitor during 3 months
### LAB TESTS IN THE PRESENCE OF EMICIZUMAB

#### Influenced in the presence of emicizumab
- aPTT
- ACT
- aPTT based one-stage single factor assays (FVIII, FIX, FXI, FXII)
- aPTT based activated Protein C resistance (APC-R)
- Bethesda assay to determine FVIII inhibitors using one-stage assay

#### No influence
- Thrombin time (TT)
- PT based one stage assays (FII, FV, FVII, FX)
- Chromogenic assays to determine single factors including FVIII (to determine endogenous or infused FVIII, inhibitor test)
- Bethesda assay to determine FVIII inhibitors using the bovine chromogenic assay
- Immune based assays (ELISA, turbidometric methods)
- Genetic tests (e.g. FV-Leiden, Prothrombin 201210 etc.)
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ITI – THE OPTIMAL TREATMENT STRATEGY FOR INHIBITOR PATIENTS

ITI today

ITI, a safe, established and effective therapeutic approach to eradicate inhibitors

• Safe management of bleeds, surgery in the absence of inhibitors

ITI tomorrow

Modified ITI strategies including emicizumab for prophylaxis in HR inhibitors

• Less burdensome ITI regimens - Optimal FVIII dose/product/frequency for ITI with emicizumab unknown

• Prevention of bleeds – impact on success rates?

• Potentially less frequent use of CVL

• Safety?

• How to maintain immune tolerance after successful ITI?
Thank you!