Inhibitor development in mild/moderate hemophilia A

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Impact of inhibitor development in MHA

- Severe complication\textsuperscript{1}
  - Aggravates bleeding pattern into severe phenotype (FVIII:C <2%)
  - Increases complications and mortality

- No standardized inhibitor eradication therapy for mild/moderate patients

- More than 30\% of all new inhibitors occur in MHA\textsuperscript{2}

\begin{itemize}
  \item Problem is substantial
  \item Neglected area of research
\end{itemize}

\textsuperscript{1} Hay et al, Thromb Haemost 1998; 79: 762–6
\textsuperscript{2} Plug et al, Blood 2004; 104: 3494-3500
• 11 countries
• 34 HTCs
• 2700 patients
INSIGHT study design

1. **Cohort study**
   Data of 2700 consecutive MHA patients treated with FVIII concentrate (1980-2010).
   
   *First results presented at ISTH:*
   - Genetic risk factors for inhibitor development.
   - Inhibitor development and mortality.
   - Cumulative incidence of viral infections and related mortality.
   - Relation F8 genotype and FVIII plasma level.

2. **Nested case-control study**
   Clinical data and DNA of 100 inhibitor patients, 400 controls matched for CED.
   
   *First results expected in 2012:*
   - Environmental & genetic risk factors for inhibitor development.

3. **TRIM: Treatment of inhibitors in MHA**
   Additional clinical data of 100 inhibitor patients.
   
   *First results presented at ISTH:*
   - Treatment during inhibitor and inhibitor eradication therapy in MHA.
Main findings:

- **F8 gene mutations** at codons 531 – 663 and 1761 – 2333 are associated with a fivefold increased risk for inhibitor development in a large unselected cohort of MHA patients.

- **Cysteine replacement** and a **positive family history** of inhibitors are other independent risk factors for inhibitor development in MHA patients.
Mortality in mild/moderate patients

Main findings:

• Inhibitor development seems to be associated with a **2 times higher risk of all-cause mortality** as compared to non-inhibitor patients.

• Major causes of death in MHA patients with inhibitors are malignancy (25%) and bleeding (19%).

• Most inhibitor patients died between year **2000 – 2007**.
Main findings:

- Most MHA inhibitor patients (74%) need treatment for bleeding or surgery during their inhibitor episode.

- In 28% of the inhibitor patients inhibitor eradication treatment is initiated by Immune Tolerance Induction or immunosuppressive treatment. This is successful in 68%.
Focus of future inhibitor research in MHA

1. **Prediction**
   - Environmental risk factors: e.g. role of intensive treatment and surgery
   - Genetic risk factors: e.g. genetic variations in immunoregulatory genes
   - Development of clinical prediction tool to estimate inhibitor risk in individual patients.

2. **Prevention**
   - Development of preventive strategies (Prophylaxis? Immunosuppressive medication? Bypassing agents? Other..)

3. **Treatment**
   - Standardized treatment guidelines for prevention/treatment of bleeding and inhibitor eradication therapy in MHA.
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