OPTIMAL USE OF COAGULATION FACTORS & IMMUNOGLOBULINS MEETING

(Kreuth III)

26-27 April 2013

Presentations

SESSION 1
“General information on the clinical use of clotting factors and immunoglobulins”

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Optimal Use of Clotting Factors and Immunoglobulins
Wildbad Kreuth, 26-27 April 2013

Welcome Address

Karl-Heinz Buchheit,
EDQM Council of Europe

Organising Institutions

• European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe
• Ludwig-Maximilian-University (LMU), Klinikum, Munich (Germany)
• Paul-Ehrlich-Institut (PEI), Langen (Germany)
Scientific Programme Committee

<table>
<thead>
<tr>
<th>LMU</th>
<th>PEI</th>
<th>EDQM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. W. Schramm</td>
<td>Prof. R. Seitz</td>
<td>Dr. M.E. Behr-Gross</td>
</tr>
<tr>
<td>Dr. K. Berger</td>
<td>Dr. A. Hilger</td>
<td>Dr. K.H. Buchheit</td>
</tr>
<tr>
<td>Dr. J. Kerr</td>
<td></td>
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</tr>
</tbody>
</table>

Prof. H.H. Peter, University of Freiburg (Germany)

Technical Organisation

Ms. F. Baumgarthen, Ms. E. Zachari (EDQM)

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Kreuth 2

Conference report

The Wildbad Kreuth initiative: European current practices and recommendations for optimal use of blood components

Karin Berger 1, Harvey G. Klein 2, Rainer Seitz 2, Wolfgang Schramm 3, Jean-Marc Spieser 2

1 University Hospital of Maribor, Department of Transfusion Medicine and Hemostasis, Maribor/University Hospital, SI-2000 Maribor, Slovenia
2 National Institute of Health, National Centre for Clinical and Laboratory Medicine, Department of Transfusion Medicine, Wroclaw, Poland
3 Paul Ehrlich Institute, Division of Hematology/Transfusion Medicine, Langen, Germany
4 Council of Europe, European Committee for the Quality of Medicines & Healthcare (EDQM), Department of Biological Standards, 28, Avenue Charles de Gaulle, 68208 Strasbourg, France

Elsevier
Jean-Marc Spieser (1949-2013)
Optimal Clinical Use of Blood and Plasma Derivatives

Background and Perspectives

Harvey G. Klein, MD
Department of Transfusion Medicine
Clinical Center
National Institutes of Health

Origins of Protein Fraction Therapy
Confluence of Need, Biology, and Technology

• 1940 - “Plasma for Britain” and Cohn Laboratory purification of proteins (Cohn et al. J Am Chem Soc 1940)
• 1944 – Cohn-Oncly (Cold ethanol) Fractionation (J Am Chem Soc 1940)
• 1947 Description of VI major fractions (Ann. Int. Med. 26: 341)
• 1949 - Cohn Fractionator (Science 1950; 112:12)
• 1955 - ADL Cohn Blood Fractionator (Tullis et al. Science 1956)
• 1975 – Kohler and Milstein Monoclonal Antibodies
• 1977 – Genentech clones Somatostatin
Cold Ethanol Fractionation
**Albumin Preparations**

- Hyperoncotic - 25%
- Hemorrhagic shock, burns
- Does not contain agglutinins
- Can be carried in backpack
- Not to exceed 250 g/48 hr
  - Responsible for 80% of intravascular colloid oncotic pressure

**Selected Protein Fraction Concentrates**

<table>
<thead>
<tr>
<th>Product</th>
<th>Daughters</th>
<th>mg/L</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>66,500</td>
<td>40,000</td>
<td>Volume replacement</td>
</tr>
<tr>
<td>Immunoglobulin (IgG)</td>
<td>150,000</td>
<td>12,500</td>
<td>Replacement; immune modulation</td>
</tr>
</tbody>
</table>

**Coagulation/Anticoagulation**

<table>
<thead>
<tr>
<th>Product</th>
<th>Daughters</th>
<th>mg/L</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (Factor I)</td>
<td>300,000</td>
<td>3,000</td>
<td>Replacement</td>
</tr>
<tr>
<td>Prothrombin (Factor II)**</td>
<td>72,000</td>
<td>150</td>
<td>Replacement</td>
</tr>
<tr>
<td>Factor V*</td>
<td>286,000</td>
<td>7</td>
<td>Replacement</td>
</tr>
<tr>
<td>Factor VII**</td>
<td>50,000</td>
<td>0.5</td>
<td>Replacement</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>331,000</td>
<td>0.3</td>
<td>Haemophilia A</td>
</tr>
<tr>
<td>Factor IX**</td>
<td>57,000</td>
<td>5</td>
<td>Haemophilia B</td>
</tr>
<tr>
<td>Factor X*</td>
<td>59,000</td>
<td>10</td>
<td>Replacement</td>
</tr>
<tr>
<td>Factor XI</td>
<td>80,000</td>
<td>5</td>
<td>Haemophilia C</td>
</tr>
<tr>
<td>Factor XII*</td>
<td>76,000</td>
<td>40</td>
<td>None</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>320,000</td>
<td>10</td>
<td>Replacement</td>
</tr>
<tr>
<td>Protein C</td>
<td>57,000</td>
<td>4</td>
<td>Replacement</td>
</tr>
<tr>
<td>Protein S*</td>
<td>60,000</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand Factor</td>
<td>220,000</td>
<td>10</td>
<td>Von Willebrand Disease</td>
</tr>
<tr>
<td><strong>Protease</strong></td>
<td>190,000</td>
<td>1</td>
<td>TTP</td>
</tr>
</tbody>
</table>

**Protease Inhibitors**

<table>
<thead>
<tr>
<th>Product</th>
<th>Daughters</th>
<th>mg/L</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1 antitrypsin</td>
<td>52,000</td>
<td>1,500</td>
<td>Replacement</td>
</tr>
<tr>
<td>C-esterase Inhibitor</td>
<td>104,000</td>
<td>170</td>
<td>Hereditary Angioedema</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>58,000</td>
<td>100</td>
<td>Replacement</td>
</tr>
</tbody>
</table>

*No commercial concentrate **Prothrombin complex ***In development
Short History of Clotting Factor Therapy

1950        Whole blood
1950-70     FFP and Cryoprecipitate
1970’s      Commercial Plasma derived Concentrates
1981        First reported AIDS cases in Hemophilia
1983        Heat-treated FVIII
1985        All Commercial concentrates heat-treated
1987        Monoclonal Factor concentrates
1992        Recombinant FVIII
1994        Recombinant IX – Albumin free
2001        2nd Generation recombinant FVIII
2003        3rd Generation recombinant FVIII

Clotting Factors

Disease Severity (genetic variant)
Prophylactic vs. Therapeutic
Nature of hemorrhage / Procedure
Factor level (therapeutic or prophylactic)
Length of treatment (prophylactic or therapeutic)
Concentrate Purity (Plasma derived vs recombinant)
and which recombinant
Immunoglobulins

Plasma Replacement therapy

IM Injection (subcut.) – specific (Tetanus, rabies, RhD, etc)

1980’s IVIg (subcutaneous) replacement in Immunodef.
   Primary (Bruton, SCID, CVID, WAS, etc.)
   Secondary (Lymphoma, Myeloma, Transplant, etc.)

1980’s – Immune modulation
   ITP, PTP, GBS, Kawasaki, Infalammatory neuropathies. MS, MGS

2000 - Subcutaneous Ig

Indications for Use

Licensed Indications
Level of Evidence
Off-label use
Rare disease - no approved medicine is available
Patients’ Rights
The transfusion of whole plasma is often unnecessary and usually inefficient

• Access to Safe, Effective Medicines
• Right Product
• Right Dose
• Right Time
• Right Indication
• Right Patient

Clinical Endpoints – Laboratory Monitoring

Parachutes reduce the risk of injury after gravitational challenge

but their effectiveness has not been proved with randomized controlled trials
What will be the Projected Demand?

You have to skate to where the puck is going, not to where it has been

Wayne Gretsky
Clinical use of immunoglobulins

HH Peter
Centre of Chronic Immunodeficiency (CCI), Freiburg

Continuous increase of indications for IVIG use*

1973
Replacement therapy in patients with hypo- or agammaglobulinemia

1981
Immunomodulatory therapy of ITP

2013

<table>
<thead>
<tr>
<th>Priority Level</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>High priority use</td>
<td>12</td>
</tr>
<tr>
<td>Medium priority use</td>
<td>18</td>
</tr>
<tr>
<td>Low priority use</td>
<td>27</td>
</tr>
<tr>
<td>Not recommended use</td>
<td>16</td>
</tr>
</tbody>
</table>

Among all therapeutic blood products IVIG is today the main driving force for an increasing demand of human plasma.

*Demand management plan for immunoglobulin use, 2012.
Department of Health PO Box 777, London SE1 6XH, UK
The total world consumption of IVIG*

![Graph showing tons of IVig from 1986 to 2010]

*Int Blood Plasma News IBPN; Imbach P, 2012; Swiss Medical Weekly 142: w13593

Demand management plan for IVIG use 2012
(Dept. Health London)

<table>
<thead>
<tr>
<th>Evidence 1A-2A</th>
<th>Evidence 2B-C</th>
<th>No evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red</strong> Priority - High</td>
<td><strong>Blue</strong> Priority - Medium</td>
<td><strong>Grey</strong> Priority - Low</td>
</tr>
<tr>
<td>Condition</td>
<td>Condition</td>
<td>Condition</td>
</tr>
<tr>
<td>Autoimmune thrombocytopenia (IgA-deposits)/nephritis*</td>
<td>Acquired red cell adhesia</td>
<td>Immune deficiency (secondary to systemic HVT infection)</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>Subacute variant(\text{HVT})</td>
<td>Autoimmune neutropenia</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Adrenocortical insufficiency</td>
<td>Autoimmune thymolysis of the synovium</td>
</tr>
<tr>
<td>Haemolytic disease of the newborn</td>
<td>Congenital factor inhibitors</td>
<td>Immune-complex glomerulonephritis</td>
</tr>
<tr>
<td>HCM is primary</td>
<td>Hydroxyurea/leflunomide and azathioprine</td>
<td>Anti-myositis antibodies</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
<td>Methotrexate</td>
<td>Anti-endothelial cell antibodies</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura (acute and persistent, excluding chronic*)</td>
<td>Methotrexate</td>
<td>Anti-thrombocytopenia antibodies</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Methotrexate</td>
<td>Anti-Jo1 antibodies</td>
</tr>
<tr>
<td>Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)</td>
<td>Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)</td>
<td>Anti-SSA/Ro antibodies</td>
</tr>
<tr>
<td>Neutrophilic dermatitis</td>
<td>Noninfective (necrotizing)</td>
<td>Anti-SSB/La antibodies</td>
</tr>
<tr>
<td>Primary immunoglobulin deficiencies</td>
<td>Paraneoplastic</td>
<td>Anti-PM-Scl antibodies</td>
</tr>
<tr>
<td>Primary antibodies deficiency</td>
<td>Primary antibodies deficiency</td>
<td>Anti-Ro/SS-A antibodies</td>
</tr>
<tr>
<td>Thrombosis with immunoglobulin deficiency</td>
<td>Secondary antibody deficiency</td>
<td>Anti-La/SS-B antibodies</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
<td>Severe or recurrent</td>
<td>Anti-Ro/SS-A antibodies</td>
</tr>
<tr>
<td><strong>Updated May 2012</strong></td>
<td></td>
<td>Anti-La/SS-B antibodies</td>
</tr>
</tbody>
</table>

DR Congo, Essential deficiencies, Nuclear hepatitis, Hepatitis B, Chronic fatigue syndrome, Critical illness. Neurosyphilis, Multiple sclerosis, Systemic vasculitis and ANCA disorders, Immune deficiency, recurrent operation in female, pregnancy loss
### Established indications for Ig treatment (Wimperis et al 2011, Deforge et al 2011)

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Selected</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunology</strong></td>
<td>Primary immunodeficiency</td>
<td>yes</td>
<td>yes/no</td>
</tr>
<tr>
<td></td>
<td>Kawasaki disease</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td>Fetal/neonatal Alloimmune thrombocytopenia (FNAIT)</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Immun thrombocytopenia (ITP)</td>
<td>selected</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Erythroblastopenia due to Parvo B19</td>
<td>selected</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>Posttransfusion purpura</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coagulation factor inhibitors (allo- and autoantibodies)</td>
<td>selected</td>
<td>no</td>
</tr>
<tr>
<td><strong>Post-HSCT in PID</strong></td>
<td></td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td><strong>Hemato-Oncology</strong></td>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td></td>
<td>Symptomatic hypogammaglobulinemia due NHL leukemia or post HSCT</td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td><strong>Neurology</strong></td>
<td><em>Guillain-Barré syndrome</em></td>
<td>selected</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td><em>Chronic inflammatory demyelinating polyneuropathy (CIDP)</em></td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td></td>
<td><em>Multifocal motor neuropathy (MMN)</em></td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td></td>
<td><em>Myasthenia gravis/ Lambert-Eaton syndrome</em></td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td></td>
<td><em>Multiple sclerosis during pregnancy</em></td>
<td>selected</td>
<td>no</td>
</tr>
<tr>
<td><strong>Rheumatology</strong></td>
<td><em>Dermatomyositis (childhood)</em></td>
<td>selected</td>
<td>selected</td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td><em>Toxic epidermal necrolysis/Stevens Johnson syndrome</em></td>
<td>selected</td>
<td>no</td>
</tr>
</tbody>
</table>

### Some emerging conditions for IVIg

(still beyond evidence 2A)*

- Systemic autoimmune diseases
  - Dermato-/Polymyositis in adults
  - SLE, catastrophic anti-phospholipid syndrome, CHB
  - Evans syndrome
  - Epidermolysis bullosa/ Steven-Johnson syndrome
  - Acquired hemophilia
  - Pure red cell aplasia
- Kidney transplantation (to reduce alloantibodies)
- Septicemia
- Acute disseminated encephalomyelitis (ADEM)
- Alzheimer’s disease
- Stiff person syndrome
- Pemphigus vulgaris

* Orange et al 2006, Deforge et al 2011, Criteria for clinical use of IVIg in Australia 2012
Mechanisms underlying immunomodulatory effects of IVIg in autoimmune disease

<table>
<thead>
<tr>
<th>Immunomodulatory mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Neutralisation of auto-antibodies (anti-idiotypes)</td>
</tr>
<tr>
<td>2 Suppression/neutralisation of pathogenic cytokines</td>
</tr>
<tr>
<td>3 Neutralisation of super-antigens</td>
</tr>
<tr>
<td>4 Down-regulation of T and B cell function, upregulation of Treg</td>
</tr>
<tr>
<td>5 Enhanced clearance of pathogenic autoantibodies via saturation of the FcRn with normal IVIg</td>
</tr>
<tr>
<td>6 Inhibitory effects of IVIg mediated via FcRIIb binding</td>
</tr>
<tr>
<td>7 Immunomodulation via IgG4</td>
</tr>
<tr>
<td>8 Blockade of CD95</td>
</tr>
</tbody>
</table>

Immunomodulatory effects of FcR
### Dual function of IgG

<table>
<thead>
<tr>
<th>A. Ig replacement therapy</th>
<th>B. Immunmodulatory therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Replacement of insufficient antibody repertoire in immunodeficiency</td>
<td>Activating or inhibiting functions of immune cells mediated via Fcγ-Rezeptor binding</td>
</tr>
<tr>
<td>b. Neutralisation of autoantibodies (Anti-idiotypic antibodies) or cytokines</td>
<td></td>
</tr>
</tbody>
</table>

**Antigen-Binding**

(Fcγ-Receptor Binding: Asn297)

### Established conditions for IVIG therapy (1A-2A)

<table>
<thead>
<tr>
<th>Primary Immundeficiency (PID)</th>
<th>Neuroimmunological diseases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute: XLA, CVID, HIM,</td>
<td>GBS, CIDP, MMN, MGS/LES, SPS, MS in pregnancy</td>
</tr>
<tr>
<td>Relative: Subclass-deficiency, SAD, THI</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Immundeficiency (SID)</th>
<th>Hematological diseases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL, NHL, MM, other related conditions</td>
<td>ITP, neonatal hemochromatosis, FNALT</td>
</tr>
<tr>
<td>Post stem cell transplantation</td>
<td>Kawasaki Syndrome</td>
</tr>
<tr>
<td></td>
<td>Inflammatory myopathies in children</td>
</tr>
</tbody>
</table>

**Dosage:**

- **PID:** 0.4g/kg every 3-4 Wo (25g/Monat).
  - continued and regular
- **SID:** 0.4g/kg every 3-4 Wo (25g/Monat) until cure of underlying disease

**Dosage:**

- **Neurology:** 0.2 - 2g/kg 2-5 days once or at irregular intervals
- **Hematology and others:** 1-2g/kg 3-5 Tage once or at irregular intervals

---

Criteria for the clinical use of IgG in Australia 2nd Edition 2012, Natl. Blood Authority, Australia
Sialic acid (SA) residue at position Asn297 of Fc-Ig promotes anti-inflammatory activity. 7-10% of IgG share the SA residue.

A summary of changes to IgG N-glycan structures that were associated with 16 loci identified through GWA study.
Lauc G et al. Plos Genetic 2013 doi:10.1371/journal.pgen.1003225.g002
**Immunmodulation through IVIg/SClg Therapy critically depends on FcR Polymorphismen**

<table>
<thead>
<tr>
<th>FcγR -Typ</th>
<th>FcγRI CD64</th>
<th>FcγRIIa CD32a</th>
<th>FcγRIIb CD32b</th>
<th>FcγRIIIa CD16a</th>
<th>FcγRIIIb CD16b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinität</td>
<td>high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Isotyp Restriction</td>
<td>IgG1</td>
<td>broad</td>
<td>broad</td>
<td>broad</td>
<td>broad</td>
</tr>
<tr>
<td>Vorkommen</td>
<td>Mac PMN Eos</td>
<td>Mac PMN Eos</td>
<td>B cells Mac</td>
<td>NK cells Eos Mac Mast cells</td>
<td>PMN</td>
</tr>
<tr>
<td>ITAM-Motife</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ITIM Motife</td>
<td></td>
<td></td>
<td>++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Two-cell model for the mechanism of IVIG activity

Nimmerjahn, F. et al. J. Exp. Med. 2007;204:11-15
Hypothesis on Immunmodulation through Fcγ-Rezeptoren (T. Kuijpers 2010)

IgG-mediated cellular functions are critically dependent on cell type and the balance between expressed inhibitory and activating FcRs.

Enhanced clearance of pathogenic autoantibodies via saturation of the FcRn with normal IVIg
Structure and binding sites of FcRn in man and rat


FcRn is a MHC I related molecule with a 30-40% sequence homology in the α-chain of MHC class I.

Function of FcRn: Recycling & transcytosis of IgG and Albumin

Relationship of serum IgG concentrations to clearance
Waldmann TA, Strober W. Metabolism of immunoglobulins. Prog Allergy. 1969; 13:1–110

FCR, fractional catabolic rate; the fraction of the serum IgG pool that disappears per day.

Conclusions

- IVIg is effective in an ever increasing number of diseases
- Besides PID and hematological conditions, autoimmune diseases represent the third group of indications for IVIg.
- Some mechanisms underlying the efficacy of IVIg in autoimmune diseases are:
  - Neutralisation of autoantibody u. cytokines,
  - Increased degradation of pathogenic antibody via saturation of FCRn with IVIg
  - Inhibitory effects of IVIg on immune cells via FcYRIIb ligation
  - Immunomodulation via IgG4
EUROPEAN SYMPOSIUM
Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

Rationale for the meeting
Clinical use of clotting factor concentrates (plasma-derived and recombinant)

Wolfgang Schramm
Ludwig-Maximilians University (LMU)
Rudolf Marx Stiftung
Munich, Germany

From Self-Sufficiency to Optimal Use of Blood and Blood Products in Europe – Initiatives from 1989 until 2009

1989
Voluntary unpaid donation
Self-Sufficiency in the EC

1994
EC Communication
Development and use of quality-assessment criteria and good practices regarding the collection, processing and transfusion of blood and blood products and patient follow-up procedures
Encouragement of health professionals to make optimal use of blood and blood products

1996
Adare, Ireland:
Blood safety and self-sufficiency is influenced by
“optimal use of these products by treating physicians taking fully into account the very special nature of their source”

1998
Vienna:
The distribution and transfusion of blood components are among the final links in the blood transfusion chain. They are concerned with both the maintenance of the quality of blood components themselves and the quality of the service in delivering and using them

1999
Wildbad Kreuth, Germany:
Rec. No 99
• ...transfusion safety should be prioritised on the basis of achievable safety gains.
• Optimising blood transfusion practices... in terms of health gain and cost benefit than additional testing strategies

2007
The EU optimal use project 2007:
The aim of this project is to encourage the optimal use of blood components across Europe through sharing of information and best practice for the benefit of patients
voluntary unpaid donation

2009
European Symposium on “Optimal Clinical Use of Blood Components” April 24th – 25th 2009
Wildbad Kreuth, Germany
Discussion of future challenges
INCREASING DIVERSITY OF FACTOR CONCENTRATES – HOW ABOUT CLINICAL USE, ACCESS FOR PROVIDER AND PATIENTS?

- A series of plasma derived and recombinant factor concentrates are licensed.
- Several innovative clotting factor concentrates are under development and clinical research. Their market licensing can be expected in the near future.

How to define optimal use?

OPTIMAL USE IS TO AVOID¹ ...

- Overuse
- Underuse
- Inappropriate use

Optimal use in haemophilia care requires² ...

... administering the right quantity of the right blood product in the right way at the right time to the right patient, and appropriate documentation of both the process and the outcome.

² Wildbad Kreuth Initiative: Conclusions and Recommendations No 71
The merits of recombinant coagulation factor concentrates over conventional plasma-derived products remain controversial. With regard to the transmission of human pathogens, it was agreed that recombinant products offer an increased margin of safety over plasma-derived products.

Incidence of inhibitors
Costs


**Recombinant - Plasma-Derived**

- Preventing spontaneous bleeding episodes
- Reducing long-term joint damage

**Further Issues:**
- Time when prophylaxis should start
- Age at which prophylaxis should be suspended
- Dosage and frequency of injections
Wildbad Kreuth Initiative 1999
Recommendations and their Translation into clinical practice

Wildbad Kreuth Initiative

• 125...registers of patients with haemophilia and related disorders should be established and maintained ...

• 126...to gather information on such patient complications as inhibitor development, allergic reactions, viral transmission and other miscellaneous adverse events.

• 127 A network of Comprehensive Care Centres (CCC) should be established in accordance with common criteria, which would provide 24-hour clinical and laboratory service and be accessible to all patients.

• 131 As a general rule, prophylactic treatment for children with severe haemophilia is recommended.

• 133 The outcome of treatment, including parameters related to quality of life and economic aspects, still needs to be assessed, and further studies, which will require funding, should be initiated.

Translation into practice

• Local and European registries have been successful established e.g:
  - EUHANET
  - UHCDO
  - DHAR

• Establishment of hemovigilance registers
  - EUHASS

• Comprehensive care centres are quite well linked

• Studies with high evidence leves have proven the outcome of prophylactic treatment in children and subsequently it is now acceptes as a general rule.

• The number of studies refering on hard outcome data and health economic aspects data is still limited

European Symposium on
“Optimal Clinical Use of Blood Components”
April 24th-25th 2009, Wildbad Kreuth, Germany

10 years after Wildbad Kreuth 1999

Since that time a tremendous number of new publications, new trends in treatment patterns, and a growing focus on economic issues have changed the environment as compared to 1999.
**Modified Recommendations on clotting factor concentrates:**

(125) Registers of patients with haemophilia and related disorders should be established and maintained in each country.

(126) Gathering **pharmacovigilance** information on such complications as inhibitor development, allergic reactions, viral transmission and other miscellaneous adverse events is mandatory. An **European initiative (EUHASS)** has recently been launched and it is hoped that this will be financed beyond the initial three year term.

(127) A network of **Comprehensive Care Centres** should be established in each country and should provide a seven days a week 24 hour clinical and laboratory service and be accessible to all patients. In order to be so designated, **such a centre** should normally provide treatment for **at least 40 patients** with severe haemophilia in order to maintain the expertise required.

**Modified Recommendations on clotting factor concentrates:**

(131) As a general rule, prophylactic treatment for children with severe haemophilia is recommended. **Ongoing prophylaxis in adults may also be considered.**

(132) Immune tolerance should be offered to all patients with haemophilia who develop clinically-significant inhibitory antibodies.

(133) Data on outcome of treatment should be collected, including clinical data such as frequency of bleedings and **assessment of joint function** as well as **quality of life and economic information.**

---

**New recommendations on clotting factor concentrates:**

**(New)** In order to foster the cooperation of patient organizations and physicians, **it is recommended that a formal mechanism be established in each country to develop best practice in hemophilia care.**

**(New)** **Home treatment** with coagulation factor concentrate should be encouraged in patients with severe haemophilia.

**(New)** **Family trees** for patients with haemophilia and other inherited bleeding disorders should be drawn up and **genetic counselling offered.**

**New recommendations on clotting factor concentrates:**

(New) Awareness should be drawn to rarer bleeding disorders which affect both men and women. Data on these patients should also be included in the national registers.

(New) Patients with rare bleeding disorders should be treated with specific coagulation factor concentrates wherever possible. The development of “orphan drugs” for the treatment of such patients should be encouraged. If fresh frozen plasma is used, it should be subjected to viral inactivation/removal treatment. Prophylaxis in patients with a severe phenotype should be considered.

(New) The European Union should foster the development of equitable care in all member states.

---


**New recommendations should be added:**

- Outcomes need to be defined and benchmarked for disease/condition specific groups, but also relevant demographic groups within populations (eg elderly, IHD)
- Outcomes need to be measured at relevant time points, including short and long-term
- Observational studies are needed to focus prospective studies on the outcome of transfusion therapy
- When evaluating plasma derived products for treating coagulation disorders, the issue of alternative strategies and their clinical relevance should be taken into consideration
- This is true for clinical outcomes as well as for cost-effectiveness issues
- The effectiveness and safety of plasma derived and recombinant products for treating coagulation disorders needs to be assessed
- This is relevant in view of the different costs of treatments with plasma derived products as compared to recombinant products
- Research funding should be committed to generate adequately powered in clinical trials.
Actual trend in pricing and reimbursement: Value Based Pricing
1st step benefit assessment, 2nd step cost assessment

**AMNOG**
Main decision criteria for price and reimbursement: Incremental patient relevant benefits compared to standard therapy (IQWIG benefit assessments, G-BA final decision)

**NICE**
"... the National Institute for Health and Clinical Excellence ... will solely give advice on the effectiveness of treatments. The move is part of the government’s previously announced plan to overhaul drug funding in the UK"

**US Comparative Effectiveness Research (CER)**
"CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care ... to assist consumers, clinicians and policy makers to make informed decisions that will improve health care not only at the individual and population level"

Clear evidence on outcomes / effectiveness (comparative effectiveness research) is a key element for access to and reimbursement of factor concentrates

**RESEARCH REQUIREMENTS TO MEET PAYERS’ REQUESTS FOR REIMBURSEMENT OF INNOVATIVE CLOTTING FACTOR CONCENTRATES**

- **Standard of care for adults?**
- **Data still insufficient?**
- **Haemophilia a rare disease?**
- **First HTA on haemophilia in Sweden?**
- **Comparative Effectiveness Research CER?**
- **High levels of evidence?**
- **Evidence Based Medicine EBM?**
- **Rising Health care costs?**
- **Scarce resources?**

**CER, EBM and HTA:**
To support decision making based on treatment benefits evaluated on high level of evidence compared to alternative or standard treatment options
Effectiveness / Benefit

1. Treatment of Life Threatening Bleed
2. Treatment of Non-Life Threatening Bleed
3. Orthopedic Operations
4. Inhibitors Against Factor VIII/IX
5. Social Integration and Prophylactic Substitution
6. Lifestyle

Units / Costs

The socio-economic reality and haemophilia treatment varies in the EU & other countries of Europe.

Haemophilia Care in Europe
Priority: Supply of factor concentrates - for all, not only in Europe – Best practice in haemophilia care

Preston Curve in 2000

(Deaton, 2004)
Comparison of GDP per capita (€) and FVIII per capita use.
Haemophilia care in Europe: a survey of 19 countries

(B. O'Mahony et al: Haemophilia, 17, 35-40, 2010)

TOPICS TO BE DISCUSSED AT THE WILDBAD KREUTH III MEETING

1. Expected additional clinical and patient relevant benefit associated with innovative clotting factor concentrates and innovative therapeutical approaches compared to standard haemophilia treatment

2. Research in haemophilia: difference between clinical trials for market authorization, investigator initiated trials and registries

3. Status quo of new therapies (patient tailored, low dose prophylaxis, gene therapy)

4. Access and requirements for reimbursement of clotting factor concentrates at present and in the future in Europe
WORKSHOP DISCUSSIONS SHOULD LEAD TO...

- Critical appraisal of status quo and identification of gaps in clinical and outcomes research in haemophilia
- Identification of future needs and to dos in haemophilia treatment and research
- Equity of haemophilia care in Europe?
Rationale for the meeting:
Regulations for plasma-derived and recombinant medicinal products

Rainer Seitz, MD
Paul-Ehrlich-Institut

EUROPEAN SYMPOSIUM
Optimal use of clotting factors and immunoglobulins
26-27 April 2013, Wildbad Kreuth, Germany

DISCLAIMER
Any opinions/recommendations presented are my own and do not necessarily reflect those of any official body

European Regulators

• Marketing authorisation
  – CP (EMA), DCP, MRP (NRA of member states)
• Blood Product Working Party (BPWP)
  – Guidelines for clinical studies, core SmPC
• Paediatric Committee (PDCO)
  – Paediatric investigation plan (PIP), input to guidelines
• Pharmacovigilance Risk Assessment Committee (PRAC)
  – Risk management plan (RMP), periodic safety update report (PSUR), post-authorisation safety studies (PASS)
Marketing Authorisation - Immunoglobulins

- Variety of safe and efficacious products authorised
- BPWP guidelines and core SmPC available (Rapporteur: J. Kerr)
- **Issues**
  - Off-label use
  - New indications
  - Supply

Marketing Authorisation - Haemophilia

- Variety of safe and efficacious plasma derived and recombinant products authorised
- BPWP guidelines and core SmPC available (Rapporteur: A. Hilger)
- **Issues**
  - Therapy modalities (e.g. continuous infusion, ITI)
  - **Novel products with e.g. prolonged half life**
    - Clinical trials according GCP
    - Safety, particularly immunogenicity?
FVIII Potency Assay

- Assessment report for Refacto AF; Procedure No. EMEA/H/C/II/59-68
  - The labelled potency of ReFacto AF is based on the European Pharmacopoeial chromogenic substrate assay, in which the manufacturing potency standard has been calibrated to the WHO International Standard using the chromogenic substrate assay. Another morococog alfa product approved for use outside Europe has a different potency assigned using a manufacturing potency standard that has been calibrated to the WHO International Standard using a one-stage clotting assay; this product is identified by the tradename XYNTHA. Due to the difference in methods used to assign product potency of XYNTHA and ReFacto AF, 1 IU of the XYNTHA product (one-stage assay calibrated) is approximately equivalent to 1.38 IU of the ReFacto AF product (chromogenic assay calibrated).

Recommendations on the potency labelling of factor VIII and factor IX concentrates

OFFICIAL COMMUNICATION OF THE SSC

A R HUBBARD1, J DODD1, T LEE1, K MERTENS1, R SEITZ2, A SRIVASTAVA2, M WEINSTEIN1ON BEHALF OF THE FACTOR VIII AND FACTOR IX SUBCOMMITTEE OF THE SCIENTIFIC AND STANDARDISATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS

doi: 10.1111/jth.12167

This paper addresses:

1. Manufacturer’s characterisation of new product potency
2. Calibration of manufacturer’s product reference
3. Manufacturer’s pharmacokinetic studies
4. Post-infusion testing in clinical laboratories
Orphan Medicinal Products

• Criteria for designating a medicinal product as an orphan medicinal product if:
  – (a) condition affecting not more than five in 10 thousand persons in the Community, or without incentives it is unlikely that the marketing in the Community would generate sufficient return to justify the necessary investment; and
  – (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Orphan Medicinal Products

• Incentives
  – Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.
  – Protocol assistance
  – Options for reduced fees, research grants
10 Designated Orphan MP for treatment of haemophilia A

<table>
<thead>
<tr>
<th>Product</th>
<th>Sponsor</th>
<th>Date of Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated rh FVIIa</td>
<td>Novo Nordisk</td>
<td>4 June 2008</td>
</tr>
<tr>
<td>Liposomal rh FVIII</td>
<td>Bayer Pharma AG</td>
<td>24 July 2009</td>
</tr>
<tr>
<td>Sequence-modified rhFVIIa</td>
<td>Bayer Pharma AG</td>
<td>9 October 2009</td>
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<tr>
<td>Recombinant porcine factor VIII (B domain deleted)</td>
<td>Inspiration Biopharmaceuticals</td>
<td>20 September 2010</td>
</tr>
<tr>
<td>Recombinant fusion protein FVIII attached to Fc of IgG1</td>
<td>Biogen Idec</td>
<td>20 September 2010</td>
</tr>
<tr>
<td>Pegylated rh BDD sequence-modified FVIII</td>
<td>Bayer Pharma AG</td>
<td>23 February 2011</td>
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<tr>
<td>Recombinant fusion protein FVIIIa with albumin</td>
<td>CSL Behring</td>
<td>15 April 2011</td>
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<tr>
<td>Pegylated rH FVIII</td>
<td>Novo Nordisk</td>
<td>26 April 2012</td>
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<tr>
<td>Vatreptacog alfa (activated)</td>
<td>Novo Nordisk</td>
<td>9 August 2012</td>
</tr>
<tr>
<td>Hum. moAb TFPI</td>
<td>Novo Nordisk</td>
<td>10 October 2012</td>
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Communication from the Commission

Guideline on aspects of the application of Article 8(1) and (2) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

The mechanism of action of an active substance is the functional description of the interaction of the substance with a pharmacological target that elicits a pharmacodynamic effect. In case the mechanism of action is not fully known, it will be for the applicant to demonstrate that the two active substances do not act via the same mechanisms.

Two active substances may only be considered to have the same mechanism of action, provided that both share the same pharmacological target and pharmacodynamic effect.

Factors not relevant to the mechanism of action are differences between two substances in terms of:
- Mode of administration;
- Pharmacokinetic properties;
- Potency; or
- Tissue distribution of the target.
Concerns

The WFH recommends that Orphan Drug designation should not be used to hinder, for the same condition or indication, the development, licensing and marketing of other products which have demonstrably different protein modification or enhancement. We see a danger that market exclusivity could create a monopoly rather than allowing for competition that will ensure the widest possible access at the most affordable prices to products which are actually different on the molecular level. Furthermore, the product with the orphan marketing authorization may not have the best efficacy or safety profile of the possible products. We urge regulators to consider these issues when deciding questions of market exclusivity for various products for the treatment of hemophilia.

This statement was approved by the WFH Blood Products Safety, Supply and Availability Committee on June 13, 2012, and adopted by the WFH Executive Committee on July 8, 2012.

EMA Response

- Market exclusivity applies only to similar MP
- CHMP decides about similarity of products
- Similar MP could still be licensed
  - with consent of MAH of original orphan
  - when MAH of original orphan is unable to produce sufficient quantities
  - when it can be established that the similar MP is safer, more effective or otherwise clinically superior
- Orphan designation is based on voluntary applications; concerns should be addressed to the applicants
Health Technology Assessment (HTA)

- Classical criteria for MA are quality, efficacy and safety of new MP
- In recent years, health care providers increasingly ask for the incremental value of a new MP for public health and individual patients
- While MA confirms that a new MP is safe and “works” as claimed, HTA takes into account medical, economic, social and ethical implications

Health Technology Assessment (HTA)

- In Germany, the Federal Joint Committee (G-BA) is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds
- One of its tasks is the benefit assessment of pharmaceuticals in accordance with the Act on the Reform of the Market for Medicinal Products (AMNOG)
- In this task, the G-BA is assisted by the Institute for Quality and Efficiency in Health Care (IQWIG), which performs analyses of the available scientific evidence
- The reimbursement of new MP is connected to the incremental benefit the applicant can document in a dossier on the basis of clinical data
Thank you for your attention!
Clinical challenges in haemophilia and access to concentrates in Europe

Dr. Paul Giangrande
Oxford Haemophilia & Thrombosis Centre
and
Nuffield Department of Clinical Medicine
University of Oxford
paul.giangrande@ndm.ox.ac.uk

Our strengths in Europe:

• Several major pharmaceutical companies and production facilities based in our continent
• Treatment usually provided free to patients (or at least at highly subsidized prices)
• Strong professional and scientific interest in haemophilia among health care professionals
  – EAHAD held first conference in 2008
• Strong and influential patient organizations (EHC)
• Widespread availability of safe treatment has improved life expectancy and quality of life
Life expectancy and haemophilia:

Haemophilia

Haemophilia Care in Europe: the ESCHQoL study

ORIGINAL ARTICLE Clinical haemophilia


Haemophilia Care in Europe: the ESCHQoL study

&Department of Transfusion Medicine and Haemostasis, University Hospital of Munich, Munich, Germany; **Department of Internal Medicine, IRCCS Fondazione Ca’ Granda Ospedale Maggiore and University of Milan, Milan, Italy; Department of Paediatrics, Lund University, Malmö University Hospital, Malmö, Sweden; **Department of Internal Medicine Research Group (MIECRG), Munich, Munich and Polyclinics of Medical Psychology, Centre of Psychosocial Medicine, University Medical Centre, Frankfurt, Frankfurt, Germany; ***Charing Cross Hospital, United Kingdom Hospitals NHS Trust, London, UK; University of Milan, Center of Pharmacoeconomics, Milan, Italy; [**]National Haemophilia Centre and Haemostasis Department, San Raffaele Clinic, Bologna, Italy; and [***]ProFacts, China, University of Medicine & Pharmacy

Summary. The aim of this study was to determine the clinical conditions of patients with haemophilia within Europe as recommended by the European Commission. In this subcategorical comparison, endurance of patients with haemophilia was assessed by the ESCHQoL study. Patients’ clinical data were collected amongst often haemophilia types, severity, treatment patterns, use of factor products, haemostatic joint scores and infections. A total of 1600 patients (95.5% with haemophilia) and 177.5% with haemophilia I were enrolled by 42 centres between 2002 and 2006. Therefore, 47.7% were children (0-12 years) and 52.3% were adults (at least 13 years). About 70% of patients had severe factor deficiency (<1%). More than half of the adults were carriers of chronic infections (12.6% 1HBs, 5.5% HIV; compared to only 3.8% children (no HBs, 7.4% HIV)). Patients were grouped according to region of residence in 2005: region 1 (N = 38.5); region 2 (N = 38); region 3 (N = 28.5). Paediatric and adult patterns in region 3 had median numbers of three and eight years, respectively. In region 1, severe haemophilia patients were more frequently treated with recombinant factor concentrates. Prophylaxis therapy was used in only 33.4% children and 33.4% adults with severe haemophilia in region 3 compared to only 95.7% and 93.4%, respectively, in region 1. Both analyses revealed that residence in areas with low factor consumption/availability is the most prominent risk factor for joint disease. Access of European patients with haemophilia to optimal care with safe factor VIII concentrates is limited and depends on the region of residence. Haemophilia, antihemophilia, clinical outcomes, European countries, factor consumption, haemophilia, severity, treatment
Haemophilia care in Europe:

• Survey of 35 countries conducted in 2012
  – Sequel to similar survey of 19 countries in 2009
• Wide range in factor VIII consumption:
  – 0.2 IU/capita (Armenia) → 8.56 (Sweden)
  – 2 IU/capita was minimum recommended national consumption at Wildbad Kreuth 2009 meeting
  – Consumption still below this in 12/35 countries
  – Consumption has risen in 15/19 surveyed in 2009
ESCHQoL study:

• Region 1: prophylaxis used in 93.7% of children with severe haemophilia and 54.1% of adults
• Region 2: prophylaxis used in 70.6% of children with severe haemophilia and 27.0% of adults
• Region 3: prophylaxis used in 31.7% of children with severe haemophilia and 8.9% of adults

ESCHQoL study:

• Data from 1400 patients in 21 European countries collected in period 2004-2006
  – 417 children (30%) and 983 adults (70%)
  – 964 (70%) had severe haemophilia (<1%)
  – 1180 (84.3%) had haemophilia A
• Patients grouped according to per capita factor consumption in country of residence:
  – Region 1: > 5 IU (A,D,DK,F,GB,S)
  – Region 2: 2-5 IU (B,FIN,GR,H,I,P,SK,SLO,S,CH)
  – Region 3: <2 IU (CZ,LT,PL,RO,TR)
EAHAD Principles of Care:

- Network of designated treatment centres
- Specialist services and emergency care
- National registries
- Central organisation with local groups
- Partnership in delivery of care
- Safe and effective treatment
- Home treatment and delivery
- Prophylaxis
- Immune tolerance for inhibitors
- Education and research
Organization of haemophilia care:

- “There are 409 known treatment centres in Europe. The size and services offered vary enormously”
- Need to define criteria for designation of haemophilia treatment centres and set standards of care throughout Europe
- Wide consultation among physicians and organizations in Europe
- Aim is to define and then designate two tiers of treatment centres in Europe (EHCC/EHTC):
  - Patient numbers will be an important criterion: 40 patients with severe haemophilia or type 3 VWD for designation as EHCC and 10 for EHTC
  - Based on self-assessment for initial 3 year period: system of external audit inspections may be established in due course
What is our goal?

• FVIII level of 1% “wholly insufficient”
• Trough level of 15% “ideal” but “unattainable in short term due to cost”
• “Improving patient quality of life should drive treatment decisions, not economics”
• “Moving forward incrementally to higher baseline levels of 3 or 5% would be a step in the right direction”
• Novel products with prolonged half-lives will facilitate this

Novel products (1):

• Clinical trials well under way and more to start soon
• Development wholly based on recombinant technology
• Products under development include:
  – Biosimilars
  – Long-acting factor VIII
  – Long-acting factor IX
  – Porcine factor VIII
  – Activated factor VII analogues
  – Anti-TFPI antibodies
  – Transgenic factor VIII & IX manufactured using animals
Novel products (2):

- I am confident that at least some of these products will be available within 5 years
- Potential to change clinical practice radically
- Success not guaranteed: several failures/problems encountered already
  - FVIII and pegylated liposomes (Bayer)
  - TFPI inhibitor (Baxter)
  - Recombinant FIX (Ipsen/Inspiration)
  - Long-acting factor VII & vatreptacog (NovoNordisk)
- Need for vigilance for unexpected problems

**Enhanced pharmacokinetic properties of a glycoPEGylated recombinant factor IX: a first human dose trial in patients with hemophilia B**

Claude Negrier,1 Karin Knobe,7 Andreas Tiede,6 Paul Giangrande,6 and Judi Moe9

1Hopital Edouard Herriot, Centre Régional de Traitement de l'Hémostase, Université Claude Bernard Lyon 1, Lyon, France; 2Möhr Centre for Thrombosis and Haemostasis, Lund University, Malmö, Sweden; 3Hematology, Haemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; 4Oxford Haemophilia & Thrombosis Centre, Churchill Hospital, Oxford, United Kingdom; and 5Department for Medical and Science, Haemophilia, Novo Nordisk A/S, Søborg, Denmark

Replacement therapy with factor IX (FIX) concentrates is the recommended treatment for patients with hemophilia B, an X-linked bleeding disorder occurring in 1:25 000 male births. N9-GP is a recombinant FIX molecule with a prolonged half-life which is obtained by site-directed glycoPEGylation where a 40-kDa polyethylene glycol molecule is attached to the activation peptide of FIX. This first human dose trial in patients with hemophilia B investigated the safety and pharmacokinetic properties of a single IV dose of N9-GP. Sixteen previously treated patients received one dose of their previous FIX product followed by one dose of N9-GP at the same dose level (25, 50, or 100 U/kg). None of the patients developed inhibitors. One patient developed transient hypersensitivity symptoms during administration of N9-GP and was excluded from pharmacokinetic analyses. In the remaining 15 patients, N9-GP was well-tolerated. The half-life was 50 hours, which was 5 times higher than the patient’s previous product. The incremental recovery of N9-GP was 94% and 20% higher compared with recombinant and plasma-derived products, respectively. These results indicate that N9-GP has the potential to reduce dosing frequency while providing effective treatment of bleeding episodes with a single dose. The trial was registered at www.clinicaltrials.gov as NCT00996346. (Blood. 2011;118(10): 2695-2701)
Summary profiles comparing N9-GP to previous FIX – normalised to 50 U/kg

![Graph](image)

Comparison of derived PK parameters between N9-GP and previous FIX:

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>N9-GP Mean (N=15)</th>
<th>rFIX Mean (N=7)</th>
<th>pdFIX Mean (N=8)</th>
<th>Ratio N9-GP/FIX</th>
</tr>
</thead>
<tbody>
<tr>
<td>t½ (hours)</td>
<td>92.7</td>
<td>19.3</td>
<td>17.8</td>
<td>5.00</td>
</tr>
<tr>
<td>Incremental Recovery (U/dL per U/kg)</td>
<td>1.33</td>
<td>0.69</td>
<td>1.12</td>
<td>1.53 (1.94; 1.20)</td>
</tr>
<tr>
<td>CL (mL/hour/kg)</td>
<td>0.70</td>
<td>6.99</td>
<td>5.48</td>
<td>0.11</td>
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<tr>
<td>Vz (mL/kg)</td>
<td>94.2</td>
<td>195</td>
<td>141</td>
<td>0.57</td>
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<tr>
<td>Time to 1% activity (days)</td>
<td>22.5</td>
<td>4.5</td>
<td>4.0</td>
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<tr>
<td>Time to 3% activity (days)</td>
<td>16.2</td>
<td>2.8</td>
<td>2.7</td>
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My predictions for the future:

• Much greater emphasis on cost effectiveness of therapy:
  – Novel products will not necessarily be adopted for routine use
  – Collection of much more outcome data (e.g. quality of life; trough levels, joint scores) will be routine
  – Much closer monitoring of factor usage by individual patients
  – Greater involvement by commercial companies in direct patient care through establishment of home care companies:
    • Offer 24-hour telephone advisory service and nurse visits

• Fewer but larger dedicated treatment centres:
  – Better distribution according to patient density
  – Significant internal migration of patients within EU to countries where better treatment is available
  – Merged adult and paediatric treatment centres
EUROPEAN SYMPOSIUM
OPTIMAL USE OF CLOTTING FACTORS AND IMMUNOGLOBULINS
26-27 APRIL 2013, WILDBAD KREUTH, GERMANY

SUMMARY OF THE EDQM SURVEY
CLOTTING FACTOR CONCENTRATES

KARIN BERGER, LMU
ANNELIESE HILGER, PEI

SURVEY EUROPEAN SYMPOSIUM „OPTIMAL USE OF CLOTTING FACTORS AND IMMUNOGLOBULINS

<table>
<thead>
<tr>
<th>Responders</th>
<th>N = 32</th>
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<td></td>
<td>Luxembourg</td>
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<td>Hungary</td>
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</table>

Area 93.8% national data

Time frame 6.3 % refer on 2010 data, 62.5 % refer on 2011 data, 31.3 % refer on 2012 data
CLOTTING FACTOR USAGE IN EUROPEAN COUNTRIES

5. Which of the following products are used to treat haemophilia in your country?

<table>
<thead>
<tr>
<th></th>
<th>Always</th>
<th>Rarely</th>
<th>Never</th>
<th>Rating Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>7.1% (2)</td>
<td>28.6% (8)</td>
<td>64.3% (18)</td>
<td>28</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>3.6% (1)</td>
<td>28.6% (8)</td>
<td>67.9% (19)</td>
<td>28</td>
</tr>
<tr>
<td>Plasma-derived Factor Concentrates</td>
<td>71.0% (22)</td>
<td>29.0% (9)</td>
<td>0.0% (0)</td>
<td>31</td>
</tr>
<tr>
<td>Recombinant Factor Concentrates</td>
<td>59.4% (19)</td>
<td>37.5% (12)</td>
<td>3.1% (1)</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td>14.3% (1)</td>
<td>14.3% (1)</td>
<td>71.4% (5)</td>
<td>7</td>
</tr>
</tbody>
</table>

PROHYLACTIC AND ON DEMAND TREATMENT

6. Are the following haemophilia treatment modalities used in your country?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Rating Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>On demand treatment</td>
<td>100.0% (32)</td>
<td>0.0% (0)</td>
<td>32</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>87.5% (28)</td>
<td>12.5% (4)</td>
<td>32</td>
</tr>
</tbody>
</table>

7. Prophylaxis in children and adults

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Between 1-25%</th>
<th>Between 26-50%</th>
<th>Between 51-75%</th>
<th>Between 76-100%</th>
<th>Rating Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>9.4% (3)</td>
<td>12.5% (4)</td>
<td>15.6% (5)</td>
<td>15.6% (5)</td>
<td>46.9% (15)</td>
<td>32</td>
</tr>
<tr>
<td>Adults</td>
<td>15.6% (5)</td>
<td>31.3% (10)</td>
<td>37.5% (12)</td>
<td>6.3% (2)</td>
<td>9.4% (3)</td>
<td>32</td>
</tr>
</tbody>
</table>
### TREATMENT STANDARDS?

**8. What determines standards of treatment?**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Rating Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>European/International guidelines</td>
<td>93.3% (28)</td>
<td>6.7% (2)</td>
<td>30</td>
</tr>
<tr>
<td>National guidelines</td>
<td>75.0% (21)</td>
<td>25.0% (7)</td>
<td>28</td>
</tr>
<tr>
<td>Centre specific guidelines</td>
<td>63.6% (14)</td>
<td>36.4% (8)</td>
<td>22</td>
</tr>
<tr>
<td>Published reports</td>
<td>70.0% (14)</td>
<td>30.0% (6)</td>
<td>20</td>
</tr>
</tbody>
</table>

### TREATMENT SETTINGS?

**9. Where are haemophilia patients generally treated?**

<table>
<thead>
<tr>
<th></th>
<th>Less than 10%</th>
<th>Between 10-50%</th>
<th>Between 51-75%</th>
<th>Between 76-100%</th>
<th>Rating Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC*</td>
<td>15.4% (4)</td>
<td>30.8% (8)</td>
<td>15.4% (4)</td>
<td>38.5% (10)</td>
<td>26</td>
</tr>
<tr>
<td>Inpatients</td>
<td>65.4% (17)</td>
<td>19.2% (5)</td>
<td>7.7% (2)</td>
<td>7.7% (2)</td>
<td>26</td>
</tr>
<tr>
<td>Outpatients</td>
<td>20.0% (5)</td>
<td>40.0% (10)</td>
<td>8.0% (2)</td>
<td>32.0% (8)</td>
<td>25</td>
</tr>
<tr>
<td>Home treatment</td>
<td>10.3% (3)</td>
<td>17.2% (5)</td>
<td>24.1% (7)</td>
<td>48.3% (14)</td>
<td>29</td>
</tr>
</tbody>
</table>

*Comprehensive Care Center
### NATIONAL HAEMOPHILIA REGISTRIES

10. Do you have a National Haemophilia Registry in your country?

<table>
<thead>
<tr>
<th></th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
</tr>
</tbody>
</table>

11. What information is covered by the National Haemophilia Registry?

<table>
<thead>
<tr>
<th>Information</th>
<th>Yes</th>
<th>No</th>
<th>Rating count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of treatment (products, modalities)</td>
<td>95.0% (19)</td>
<td>5.0% (1)</td>
<td>20</td>
</tr>
<tr>
<td>Documentation of outcomes / complications</td>
<td>80.0% (16)</td>
<td>20.0% (4)</td>
<td>20</td>
</tr>
<tr>
<td>Documentation of quality of life</td>
<td>42.1% (8)</td>
<td>57.9% (11)</td>
<td>19</td>
</tr>
<tr>
<td>Reimbursement of haemophilia treatment linked to participation</td>
<td>29.4% (5)</td>
<td>70.6% (12)</td>
<td>17</td>
</tr>
<tr>
<td>Published Reports</td>
<td>38.9% (7)</td>
<td>61.1% (11)</td>
<td>18</td>
</tr>
</tbody>
</table>

### MANAGEMENT OF HAEMOPHILIA REGISTRY?

12. Who manages the National Haemophilia Registry?

<table>
<thead>
<tr>
<th>Manager</th>
<th>Response Percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>14.3%</td>
<td>3</td>
</tr>
<tr>
<td>Academic Organisation</td>
<td>23.8%</td>
<td>5</td>
</tr>
<tr>
<td>Clinician(s)</td>
<td>76.2%</td>
<td>16</td>
</tr>
<tr>
<td>Haemophilia Patient Organisation</td>
<td>42.9%</td>
<td>9</td>
</tr>
<tr>
<td>Industry</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>14.3%</td>
<td>3</td>
</tr>
</tbody>
</table>
### PURCHASING CLOTTING FACTOR CONCENTRATES?

#### 13. Is there a National Tender for the procurement of Coagulation Factor Concentrates in your country?

<table>
<thead>
<tr>
<th>Response</th>
<th>Percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>56.3%</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>43.8%</td>
<td>14</td>
</tr>
</tbody>
</table>

#### 14. Which organisation purchases Haemophilia products in your country?

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Response Percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Government</td>
<td>21.9%</td>
<td>7</td>
</tr>
<tr>
<td>National Health care System</td>
<td>50.0%</td>
<td>16</td>
</tr>
<tr>
<td>Health care providers</td>
<td>31.3%</td>
<td>10</td>
</tr>
<tr>
<td>Haemophilia Patient Organisation</td>
<td>3.1%</td>
<td>1</td>
</tr>
<tr>
<td>Health Insurance companies</td>
<td>25.0%</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>12.5%</td>
<td>4</td>
</tr>
</tbody>
</table>
Wildbad Kreuth III
Summary of Immunoglobulin Survey

General (34/34)

• 34/43 Countries: Europe, USA, New Zealand and Japan
• Time frame: 94% data from 2011 – 2013
• Area: 85% national data
  6% regional data
  9% local data
• Specialisation: 40 % Immunodeficiency
  60 % Transfusion/haemovigilance
• Organisation: 18 university hospitals or medical institutes
  10 transfusion/blood supply centres
  4 Ministries of Health (ES, GR, LI, SER)
  2 agencies (USA, BE)
• Standard of treatment: ~85% European/International GL + publ. reports
  77% Nat. GL
  68% Centre GL
Ig Use in Countries (33/34)

- All listed brands were 100% available for ID
- All listed brands were 20-90% available for established non-ID
- 16 “other“ brands, (3/16 other national names)

Purchasing Ig (32/34)

- National tender?  
  - 37.5% yes  
  - 62.5% no

- Which organisation?
  - 53% Health care providers
  - 28% Other (mainly hospitals)
  - 16% Immunodeficiency centres
  - 9% Insurances
PID

- Where? 30/34
  13/19 – (68%) > 51% care centres
  12/22 – (55%) < 10% inpatients
  8/21 – (38%) > 51% outpatients
  7/18 – (39%) > 51% home treatment

- ID registry? 33/34
  48.5% yes (11/15 nat., 12/15 ESID, 5 „other“)
  51.5% no

- Nat. Registry
  - Which info? 13/34
    100% treatment modalities
    77% outcomes/complications
    46% QOL
    23% published reports
  - Management 14/34
    57% clinician
    29% government
    21% academic organisation
    14% patient organisation

Licensed vs. off-label (33/34)

Off-label reimbursed? 19 yes (16/19 most indications, with restrictions)
14 no