NEW PRODUCTS FOR TREATMENT OF HEMOPHILIA
- CHANGING OPTIONS

and

- CLINICAL TRIAL DESIGN

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<td>Research Support:</td>
<td>Dr. Jerry Powell has the following relationships to disclose: investigator for clinical trials funded by Bayer HealthCare Pharmaceuticals, Biogen Idec, Baxter, CSL Behring, Octapharma, and NovoNordisk</td>
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History of Hemophilia in California:

1964 – 1978
Plasma Factor VIII purified and used to treat hemophilia
cryoprecipitate

Major Milestones: 1979 to present -

- “cryo” – Judith Graham Poole
- Factor VIII gene identified
- Factor VIII gene cloned
- Recombinant Factor produced – 1992
- Prophylaxis
- Next step: long acting factors

Today, “the most exciting time in hemophilia in 25 years”

Thank you patients for your encouragement for research, and for enthusiastic participation in clinical trials
Treatment of HEMOPHILIA

“Focus on goal” built the Golden Gate Bridge and won the America’s Cup,

and it can get a clinical trial completed scientifically

“Evidence based clinical trial design”
What is the “goal” for a clinical trial?

- Does the patient* want to use the new factor product.

or

- Efficacy
- Safety

* Should anyone else be allowed to have decision authority?
Hemophilia is “deficiency of a clotting factor”

1. Normal is > 50 %
2. Need normal for surgery

Spontaneous bleeding occurs when < 2 %.

FIBRINOGEN → FIBRIN (I)
Monomer → Cross-linked
Pharmacokinetic Properties

- FVIII plasma concentrations between treatment groups

**Plasma Concentration** One-stage Assay (n = 12 per group unless otherwise indicated)

Half life = 9.4 hours

History of hemophilia clinical trials
“evidence based clinical trial design”

- Over 30 years of zero problems
- More than a dozen plasma-derived products
- More than 6 recombinant factor products
- All studies for FDA or EMEA approval involved dozens of subjects

Simple Focus on Factor level and safety
Design of clinical trials for long acting Factor products

- Data collected for efficacy
- Data collected for safety

The point here is that collecting “interesting” but extraneous data is inappropriate and unscientific. One should not try to perform overly complicated experiments.
The study included:
(i) a single pharmacokinetic study in 18 previously treated patients, comparing lots of the unheated (Koate(R)-HP) and the heat-treated preparation, and
(ii) extended home treatment for 36 patients to assess immunogenicity.
What is the goal?

The study included: (i) a single pharmacokinetic study in 18 previously treated patients, comparing lots of the unheated (Koate(R)-HP) and the heat-treated preparation, and (ii) extended home treatment for 36 patients to assess immunogenicity.

Simplicity = “what is the critical parameter to measure?”

= “collect only critical data”

patient assessment
safety

no Gilbert score, no QOL, no personal information, minimal details of bleed, minimal intrusion in life
What is the expected life of someone without factor treatment? 1960’s…..

- Most died by 20 years of age
- Head bleeds and brain damage
- Ruined joints

simple replacement was the goal
Hemophilia

All severe patients

1 in 200 severe patients per year
More hemophilia...

Result of spontaneous bleeding
Into knee joint
Blood is highly inflammatory
Aggressive on-demand treatment of spontaneous bleeding 1990’s.....

- Most live close to normal life expectancy
- Head bleeds and brain damage
- Ruined joints, later in life

Now we have prophylaxis, generally 3 times per week
Clinical Trial Design for Parachutes

Need a control group?
Progress in clinical trials for hemophilia

• Zero safety concerns
• Life expectancy from 20 years of age to essentially normal life expectancy

No other genetic disease has achieved this tremendous progress.... So the question is “why?“

1. Interested, educated enthusiastic patients
2. Simplicity of clinical trial design
1. Identify which factor is missing:
2. What Factor IX concentration is needed?
NEW PRODUCTS FOR TREATMENT OF HEMOPHILIA

1. Same Factor molecule, new manufacture company. In clinical trials
2. Altered Factor molecule, longer half-life. In clinical trials
3. Different approach to providing clot
LipLong

1. First trial randomized prospective
2. Largest clinical trial
3. Shifted paradigm for treatment approaches
BAY 79-4980

rFVIII-FS non-covalently attached to polyethylene glycol (PEG) on the outer surface of liposomes.

rFIX-Fc Fusion Protein

Immunoglobulin structure
rFVIII-Fc Fusion Protein

Several recombinant Fc fusion proteins developed by other companies and approved for clinical use.

Monomer technology has been applied to FVIII for the treatment of hemophilia A

- Single B-domain-deleted rFVIII fused to dimeric Fc region of human IgG$_1$
- Specific activity and post-translational modifications of rFVIII-Fc comparable to wild type FVIII
- Comparable activity in 1-stage aPTT and 2-stage Chromogenic assays
Altered surface molecules

1. Site specific pegylation
2. glycopegylation
3. other
Clinical trials in Previously Treated Patients (PTPs)

1. Inhibitors occur within the first 9 infusions

2. Community working together
   1. Enthusiasm
   2. Investigators working together
   3. Manufacturers working together with investigators
   4. All working with regulatory agencies

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Clinical trials in Previously Treated Patients (PTPs)

1. Test safety, then move forward with post-marketing surveillance inhibitors?

2. Shifted paradigm for treatment approaches, long-acting Factors,

   Factor level predicts outcome

But, efficacy remains: patient choice

   excellent
   good
   moderate
   none, poor
The future?

Role of SSC in scientific design and harmonization

Enlarge the pool of patients who can participate:
< 2%, not the restrictive < 1%

1. Define criteria for trials
   1. Focus = factor level
   2. Simple = patient assessment
   3. Efficacy and safety
      1. 20 days of exposure, not 50
      2. Each day of factor level above 10%

2. FDA listens

   Today, “the most exciting time in hemophilia in 25 years”

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Any questions?