Evolving perspectives on access to hemophilia treatment

The best is yet to come

Albert Farrugia
WFH Global Forum
Montreal
September 26, 2013
THE VIEWS IN THIS PRESENTATION ARE ENTIRELY MY OWN, AND DO NOT REPRESENT THOSE OF ANY ORGANIZATIONS I AM AFFILIATED TO
AF and the GF
2000 - 2013

• 1\textsuperscript{st} GF – Self Sufficiency
• 2\textsuperscript{nd} GF - Regulation
• 3\textsuperscript{rd} GF – Cryo
• 4\textsuperscript{th} GF – Regulation
• 5\textsuperscript{th} GF - Biosimilars
• 6\textsuperscript{th} GF – vCJD
• 7\textsuperscript{th} GF – HTAs
• 8\textsuperscript{th} GF - Economic considerations – pricing, sustainability, access, increased supply? (???)
Economists

“Jeremy refuses to study. He says he’s going to become an economist and they don’t have to know anything.”
Hemophilia is a (rare) medical success story

- Hemophilia
- Cystic fibrosis
- Thalassemia major
- Muscular dystrophy

Life expectancy in Hemophilia

- ~75 years
- ~37 years
- ~30 years
- ~10-20 years
Prevalence of Haemophilia A

Effect of FVIII usage

- Survival from worse effects
- Adequate episodic therapy
- Joint surgery
- Secondary prophylaxis in children
- Primary prophylaxis with current protocols
- Tolerization
- Increased prophylaxis dosage
- Prophylaxis throughout life
Worrisome words

- “an acceptable frequency of bleeds”
- “adequate preservation of joint function”
- “prophylaxis should be commenced after the second joint bleed”

Etc etc
I want to make three points

• We need *more* treatment product

• There *is* more treatment product

• We *can* have more treatment product
WE NEED **MORE** TREATMENT PRODUCT
The rich and the poor

70% of the world’s hemophilia population receives no or inadequate treatment (?)
After the viral safety problems, men with hemophilia are approaching a normal life expectancy

But bleeding is still a killer!
Haemophilia patients in Sweden

<table>
<thead>
<tr>
<th>Causes of death in haemophilia in Sweden – HIV and HCV excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia %</td>
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<tr>
<td>----------------</td>
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<tr>
<td>Total deaths</td>
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<tr>
<td>Malignancies</td>
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<tr>
<td>Hemorrhagic</td>
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<tr>
<td>Ischaemic heart disease</td>
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<tr>
<td>Cardiovascular disease</td>
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</tbody>
</table>
The future for Hemophilia
Higher dosages

Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels

Den Uijl et al Haemophilia Volume 17, Issue 1, pages 41-44
Risk of ICH in Italian haemophiliacs

Relationship to age

% Relative risk to reference

Age [years]

Risk first decreases, then *increases* with age

THERE IS MORE TREATMENT PRODUCT
The scarcity paradigm

• The haemophilia landscape has been shaped by
  – A perception of safety
  – A perception of costs
  – A perception of scarcity

• Safety is now not an issue (???)

• The question of costs is related to that of scarcity

• With the advent of increasing numbers and quantities of FVIII, there is unlimited potential for the production of FVIII

• We need to break out of the scarcity paradigm
Demand for FVIII 1980-2010

NB – in 2010, ca 3000 IU pd FVIII consumed
We can get more.....

**Plasma-derived FVIII**

- In 2010, ca 3B IUs of pd FVIII consumed
- In 2010, ca 3000 tonnes plasma fractionated
- Estimate only ca 50% of the plasma was used to extract FVIII
  - Situation not very different from 35 years ago
  - Not necessarily reflective of “cryo wastage”
We can get more.....

Recombinant FVIII

• Supply theoretically infinite (keep feeding the cells)
• What is the current yield from rVIII manufacture?
  – No public information
  – Supply has continued to increase steadily
  – Number of players constant over past 10 years (about to change?)
  – Safe to assume manufacturing efficiency has increased
• ALSO - many published improvements
Lentiviral Vector Platform for Production of Bioengineered Recombinant Coagulation Factor VIII

H Trent Spencer¹, Gabriela Denning², Richard E Gautney², Boro Dropulic³, Andre J Roy³, Lajos Barany⁴, Bagirath Gangadharan¹, Ernest T Parker¹, Pete Lollar¹ and Christopher B Doering¹

¹Aflac Cancer Center and Blood Disorders Service, Department of Pediatrics, Emory University School of Medicine and Children’s Healthcare of Atlanta, Atlanta, Georgia, USA; ²Expression Therapeutics, LLC., Tucker, Georgia, USA; ³Lonza Corporation, Gaithersburg, Maryland, USA

Herein, we describe the development of a bioengineered fVIII product using a novel lentiviral-driven recombinant protein manufacturing platform. The combined implementation of these technologies yielded production cell lines that biosynthesize in excess of 2.5 mg/l of recombinant fVIII at the rate of 9 pg/cell/day, which is the highest level of recombinant fVIII production reported to date.
Bioengineering strategies lead to synergistic improvements in FVIII secretion efficiency

* $p < 0.05$

Strategies for therapeutic enhancement

Half-life extension

PEGylated Liposomes

PEGylation
- Random
- Site specific

Fusion protein
- Fc fragment
- Albumin

Modification of amino acid sequence

Peyvandi F.
Results of Long acting products
- Clinical studies -

Factor IX  3 to 5-fold

Factor VIII  1.5 to 1.8-fold

rFVIIa  3 to 5-fold

Peyvandi F.

- rFIX-Fc fusion
- rFIX glycoPEGylated
- rFIX-albumin fusion

- rFVIII-Fc fusion
- rFVIII-glycoPEGylated

- rFVIIa glycoPEGylated
- rFVIIa variant with 4 amino acid changes
“Knowledge of individual patient FVIII half-life with these products would appear to be even more important than with conventional products when designing prophylactic regimens. This needs to be taken into account when clinical trials with these products are devised and it is unlikely that once weekly infusions will be suitable for all patients.”
WE **CAN** HAVE MORE TREATMENT PRODUCT
Cost Effectiveness of prophylaxis vs on-demand treatment for hemophilia A

- Coalition of PPTA, treaters and patients
- Used latest best evidence for effectiveness of prophylaxis
- Used patient survey for benefit
- Used modern concept for discounting

<table>
<thead>
<tr>
<th>Payer Perspective</th>
<th>Cost Effectiveness</th>
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<tbody>
<tr>
<td>UK</td>
<td>Prophylaxis is DOMINANT over On Demand</td>
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<tr>
<td>USA</td>
<td>Cost/QALY is $68K (Cost-effective)</td>
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<tr>
<td>Sweden (daily prophylaxis)</td>
<td>Prophylaxis is DOMINANT over On Demand</td>
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Farrugia et al *Haemophilia* in press 2013
## Outcomes of the cost-utility model

<table>
<thead>
<tr>
<th>Payer Perspective</th>
<th>Cost</th>
<th>QALYs</th>
<th>Incremental Cost</th>
<th>Incremental QALYs</th>
<th>Cost/QALY</th>
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<td><strong>Sweden (Daily Pro dosing)</strong></td>
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<td>OD</td>
<td>SEK 22,101,124</td>
<td>17.87</td>
<td>- SEK 10,541,993</td>
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<td>28.87</td>
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<td>SEK 400,386</td>
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ORIGINAL ARTICLE

Treatment for life for severe haemophilia A—A cost-utility model for prophylaxis vs. on-demand treatment

A. FARRUGIA,†† J. CASSAR,§ M. C. KIMBER,∥ M. BANSAL,∥∥ K. FISCHER,¶ G. AUSERSWALD,∥∥∥ B. O’MAHONY,†† K. TOLLEY,∥∥∥ D. NOONE∥∥∥ and S. BALBONI∥∥∥

*Plasma Protein Therapeutics Association, Annapolis, MD, USA; †School of Surgery, University of Western Australia, Crawley, Western Australia; ‡School of Medicine, Australian National University, Canberra, Australia; §Faculty of Health, University of Canberra, Canberra, Australia; ¶Van Creveldkliniek, University Medical Center Utrecht, Utrecht, The Netherlands; ∥∥ Ambulanz fuer Thrombose und Haemostasestorungen Prof.- Hess Kinderklinik, Klinikum Bremen-Mitte, Germany; ††Irish Haemophilia Society, Dublin, Ireland; and ‡‡Tolley Health Economics Ltd, Derbyshire, UK
Analysis of rVIII price in USA 2002

Average Unit Price of Recombinant Products

NB – initial price

Thromb Haemost 2002; 88: 545–53
• The cumulative rate of inflation in the USA between 1993 and 2013 was 61.7 %
• On this basis, if the price of rVIII had remained constant, today one IU of rVIII would cost $1.45
MANDATORY READING

Haemophilia (2013), 19, 660–667

DOI: 10.1111/hae.12169

REVIEW ARTICLE

Purchasing factor concentrates in the 21st century through competitive tendering

C. R. M. HAY*

*The UK National Haemophilia Database, Manchester, UK; and †Department of Haematology, Manchester University, Manchester, UK
“The dip in usage in 2001 corresponded to the interruption in supply of Kogenate and Helixate, which halved the UK supply of rFVIII for 18 months, highlighting the importance of security of supply.”
UK purchase process

Recombinant Factor VIII eAuction

- Company 1
- Company 2
- Company 3
- Company 4

Time:
09:00, 09:01, 09:02, 09:03, 09:22, 09:24, 11:10, 11:19, 11:24

Price (Pence):
35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45
Price of factor concentrates in Brazil

![Bar chart showing the price of factor concentrates in Brazil from 1997 to 2004. The chart compares FVIII and FIX over the years. The price decreases over time.]
We need to **grow the cake**

Current FVIII usage

- Etc etc
- Higher dosages
- Life long prophylaxis
- More access globally
Elasticity of demand

(a) Perfectly inelastic demand
(b) Unit elastic demand
(c) Perfectly elastic demand
Pizza

(a) Large price change and small quantity change

(b) Small price change and large quantity change
Emerging approaches

• Assessment of elasticity
• Budget impact analysis
• ............
Responses

• “an acceptable frequency of bleeds”
  – ZERO

• “adequate preservation of joint function”
  – NORMAL

• “prophylaxis should be commenced after the second joint bleed”
  – AT DIAGNOSIS
Final reflections – for today

• We’ve gone a long way – we have a long way to go
• As clinical research continues, we see that more product is needed
• The supply of all forms of FVIII has increased over the past years
• Treatment of FVIII to optimal levels is cost-effective
• While prices remain high, there has been a steady decrease
• If consumption rises to approach the real demand for FVIII, prices may be expected to drop further
“..the way is long, but the end is near
Already the fiesta has begun,
The face of God will appear.....”

Dylan 1975