Cellular, Gene, and Blood Products for Rare Diseases: Challenges and Opportunities

John Hyde, PhD, MD
Office of Cellular, Tissue, and Gene Therapy
CBER
Learning Objectives

• Summarize biologics effectiveness criteria
• Review examples of recent CBER approvals using small trials
• Consider factors affecting clinical development of cellular and gene products
• Learn about some of the opportunities presented by cellular and gene therapies for treatment of rare diseases
Effectiveness for Biologics

• Controlled clinical investigations
  – unless waived as not applicable or essential

• Alternate methods may be adequate:
  – serological response in clinical studies
  – animal and other laboratory assay evaluations
  – where a previously accepted correlation with clinical effectiveness already exists
  – corroborated by other clinical studies or data
Case Studies

- Ceprotin (Protein C), 2007
  - Historical control
- ATryn (Anti-thrombin), 2009
  - Historical active control
- RiaSTAP (Fibrinogen concentrate), 2009
  - Accelerated approval using surrogate
Case Studies (cont.)

• Anascorp (Scorpion anti-venom), 2011
  – Concurrent control

• Corifact (Factor XIII), 2011
  – Accelerated approval using surrogate
Ceprotin

• Protein C concentrate (human)
• For severe congenital protein C deficiency
• Patients have acute episodes of purpura fulminans (PF), warfarin-induced skin necrosis, or other thrombotic events
• Pivotal study was open-label, nonrandomized trial in 18 subjects
Ceprotin

• Compared treatment of 18 episodes PF vs. 11 historical control episodes using FFP or anti-coagulants
  – Higher rate of effective w/o complications

• Safety data from
  – Short- and long-term prophylaxis
  – patients treated under emergency IND
  – additional subjects with varied exposures
ATryn

• Recombinant anti-thrombin (AT) III from goats
• For prevention of peri-operative and peri-partum thromboembolic events in hereditary AT deficiency
ATryn

- Approval based on data from two efficacy studies (total N=31) compared to historical data with plasma-derived AT III (N=35)
- Non-inferiority criterion was met
- Additional safety data being obtained via post-marketing registry
RiaSTAP

• Fibrinogen concentrate (human)
• For congenital fibrinogen deficiency
• Open-label study using pre- vs. post-infusion clot firmness as surrogate (N=15)
• Clear-cut effect – differences highly statistically significant
• Supporting clinical data from historical studies, foreign marketing experience
RiaSTAP

• Accelerated approval
• Verification study to confirm significance of surrogate findings for hemostatic efficacy
• Verification study also to compare acute bleeding episodes in 23 subjects vs. episodes in 39 patients treated with cryoprecipitate
Anascorp

• Equine Fab scorpion anti-venom
• For scorpion envenomation
• Pivotal trial: R, DB, PL-C, pediatric
  – 8 treated vs. 7 placebo,
• Endpoint: resolution of pathologic agitation within 4 hours
Anascorp

• Difference in success percentage was stat. signif. and met clinical superiority criterion of ≥ 20%
• Supported by open-label data, ex US experience
• Safety from large uncontrolled safety database
Corifact

- Factor XIII concentrate (human)
- For congenital F XIII deficiency
- Considerations:
  - Mechanisms of action well understood
  - Safe and effective in rat knockout model
- Open-label study in 13 subjects using F XIII trough levels as surrogate
Corifact

• Accelerated approval
• Postmarket validation study to correlate trough levels and clinical efficacy
• Safety in 12 clinical studies, 187 subjects (not all F XIII deficient) + ex US safety
• Identified risks were as expected from other plasma-derived & factor replacement products
Features That Have Made the Use of Small Trials Feasible

- Potential for large effect size with some products
- Historical data available for some diseases
- Predictive animal models available for some diseases
- Understanding of mechanistic basis, role of biomarkers
Challenges
(Particularly for Cellular & Gene Products)

- Technical
  - Novelty and complexity of products, demands on manufacturing
- Relevant animal models may be lacking
- Invasive procedures may be required
- Persistent or permanent effect
  - May be a goal, but can “use up” patients
- Immune responses
Challenges

• For cellular therapies
  – Mode of action may not be clear
  – Uncertainty about what is effective cell type
  – Potential for undesired differentiation, migration, function
  – Tumors or ectopic tissue
  – Graft vs. host disease if lymphoid component
Challenges

• For gene therapies
  – Altered expression of recipient’s genes
  – Mutagenesis
  – Uncontrolled expression
  – Immune reaction to vector
Challenges

• Safety setbacks
  – Fatal reaction to a gene therapy: Jesse Gelsinger case
  – Brain tumor with neural stem cells
  – Leukemia with X-SCID gene therapy
Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer

Steven E. Raper, a Narendra Chirmule, b Frank S. Lee, c Nelson A. Wivel, b Adam Bagg, c Guang-ping Gao, b James M. Wilson, b and Mark L. Batshaw d,*

a Department of Surgery, University of Pennsylvania School of Medicine, BRB II/III Rm., 607 421 Curie Blvd., Philadelphia, PA 19104, USA
b Department of Medicine, University of Pennsylvania School of Medicine, 36th & Spruce Streets, Philadelphia, PA 19104, USA
c Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, 605 BRB II/6100, 4200 Curie Blvd., Philadelphia, PA 19104, USA
d Department of Pediatrics, Children’s Research Institute, Children’s National Medical Center, George Washington School of Medicine and Health Sciences, 111 Michigan Avenue, N.W. Washington, DC 20010, USA

Received 30 May 2003; received in revised form 8 August 2003; accepted 11 August 2003
Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio¹,², Abraham Hirshberg³, Bernd W. Scheithauer⁴, Yoram Cohen¹, Ron Loewenthal⁵, Luba Trakhtenbrot², Nurit Paz¹, Maya Koren-Michowitz², Dalia Waldman⁶, Leonor Leider-Trejo⁷, Amos Toren⁶, Shlomi Constantini⁸, Gideon Rechavi¹,⁶*

¹ Cancer Research Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ² Institute of Hematology, Sheba Medical Center, Tel Hashomer, Israel, ³ Department of Oral Pathology, School of Dental Medicine, Tel Aviv University, Tel-Aviv, Israel, ⁴ Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, United States of America, ⁵ Tissue Typing Laboratory, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ⁶ Department of Pediatric Hemato-Oncology, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel, ⁷ Institute of Pathology, Tel-Aviv Medical Center, Tel-Aviv, Israel, ⁸ Pediatric Neurosurgery, Dana Children's Hospital, Tel-Aviv Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel
LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1

S. Hacein-Bey-Abina,¹,²*, C. Von Kalle,⁶,⁷,⁸ M. Schmidt,⁶,⁷ M. P. McCormack,⁹ N. Wulffraat,¹⁰ P. Leboulch,¹¹ A. Lim,¹² C. S. Osborne,¹³ R. Pawliuk,¹¹ E. Morillon,² R. Sorensen,¹⁹ A. Forster,⁹ P. Fraser,¹³ J. I. Cohen,¹⁵ G. de Saint Basile,¹ I. Alexander,¹⁶ U. Wintergerst,¹⁷ T. Frebourg,¹⁸ A. Aurias,¹⁹ D. Stoppa-Lyonnet,²⁰ S. Romana,³ I. Radford-Weiss,³ F. Gross,² F. Valensi,⁴ E. Delabesse,⁴ E. Macintyre,⁴ F. Sigaux,²⁰ J. Soulier,²¹ L. E. Leiva,¹⁴ M. Wissler,⁶,⁷ C. Prinz,⁶,⁷ T. H. Rabbitts,⁹ F. Le Deist,¹ A. Fischer,¹,⁵†† M. Cavazzana-Calvo¹,²†
Opportunities

• Primary Immunodeficiency (gene-modified cellular therapy)
• Hemophilia B (gene therapy)
• Leber’s Congenital Amaurosis (gene therapy)
Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

Factor IX Activity Following Gene Therapy for Hemophilia B
Human RPE65 Gene Therapy for Leber Congenital Amaurosis: Persistence of Early Visual Improvements and Safety at 1 Year

Artur V. Cideciyan, William W. Hauswirth, Tomas S. Aleman, Shalesh Kaushal, Sharon B. Schwartz, Sanford L. Boye, Elizabeth A.M. Windsor, Thomas J. Conlon, Alexander Sumaroka, Ji-jing Pang, Alejandro J. Roman, Barry J. Byrne, and Samuel G. Jacobson

![Graph showing visual acuity over time for different study eyes (P1, P2, P3).](image)
Challenge Question 1

Examples of recent approvals of biologic products in CBER for rare diseases included all of the following except:

a. Use of concurrently controlled clinical trial
b. Use of open-label trial and historical control
c. Use of the effectiveness requirement waiver
d. Use of a surrogate endpoint for accelerated approval
Challenge Question 2

The following feature of cellular or gene products is a greater challenge to development in very rare diseases than in non-rare diseases:

a. Gene effect might be transient due to cell division
b. Effect might be persistent or permanent
c. Invasive administration might be needed
d. Product might have large effect size
OCTGT Contact Information

• John Hyde
  john.hyde@fda.hhs.gov

• Regulatory Questions:
  Contact the Regulatory Management Staff in OCTGT at
  CBEROCTGTRMS@fda.hhs.gov
  or Lori.Tull@fda.hhs.gov
  or by calling (301) 827-6536

• OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/
  ucm232821.htm
Public Access to CBER

CBER website:  
http://www.fda.gov/BiologicsBloodVaccines/default.htm

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)  
Email: ocod@fda.hhs.gov  
Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)  
Email: industry.biologics@fda.gov  
Phone: 301-827-4081

Follow us on Twitter  
https://www.twitter.com/fdacber