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

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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 $\geq$ 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

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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

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LMO2-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1

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Opportunities

- Primary Immunodeficiency (gene-modified cellular therapy)
- Hemophilia B (gene therapy)
- Leber's Congenital Amaurosis (gene therapy)

ESTABLISHED IN 1812 DECEMBER 22, 2011 VOL. 365 NO. 25

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B

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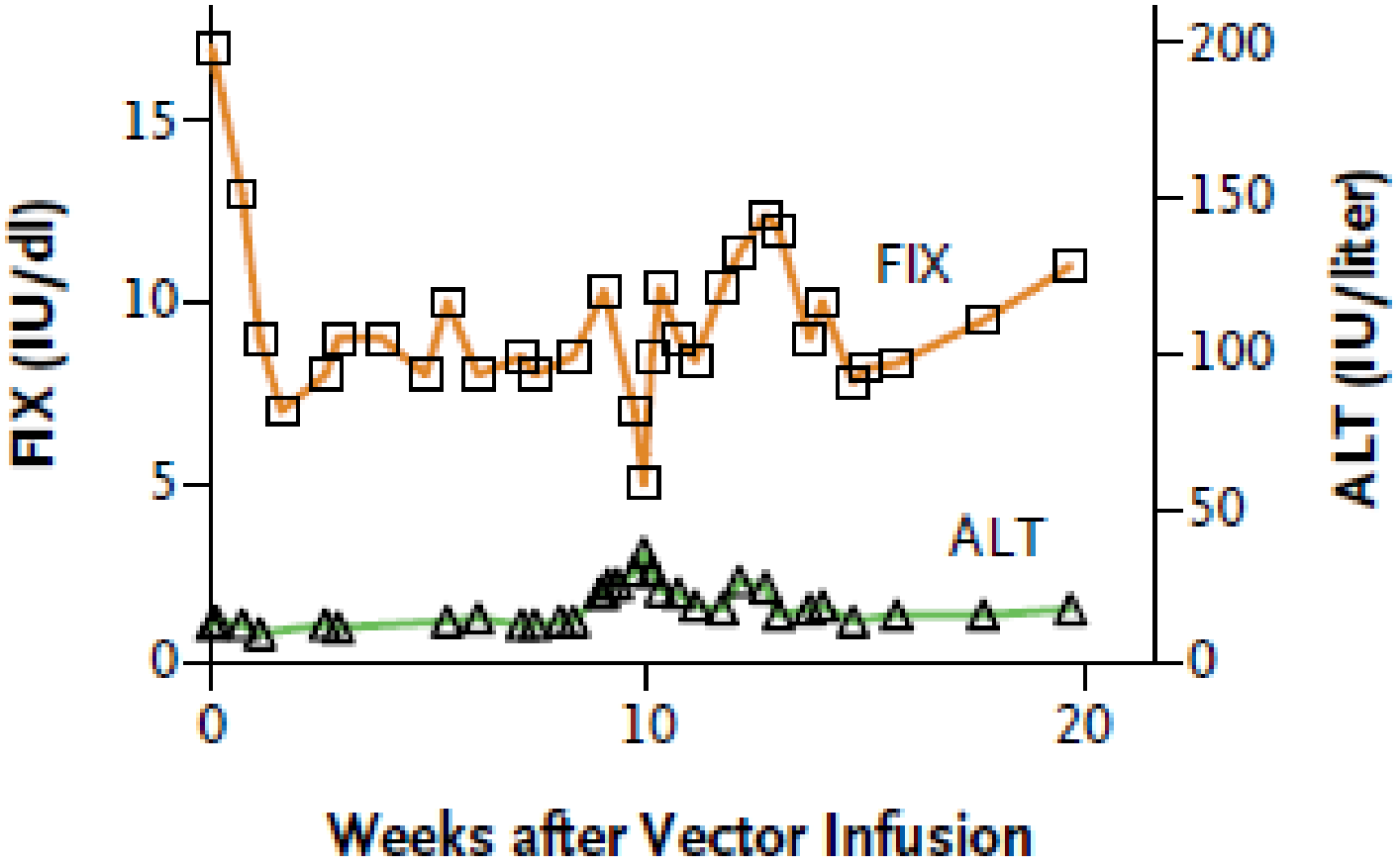
Factor IX Activity Following Gene Therapy for Hemophilia B



Human *RPE65* Gene Therapy for Leber Congenital Amaurosis: Persistence of Early Visual Improvements and Safety at 1 Year

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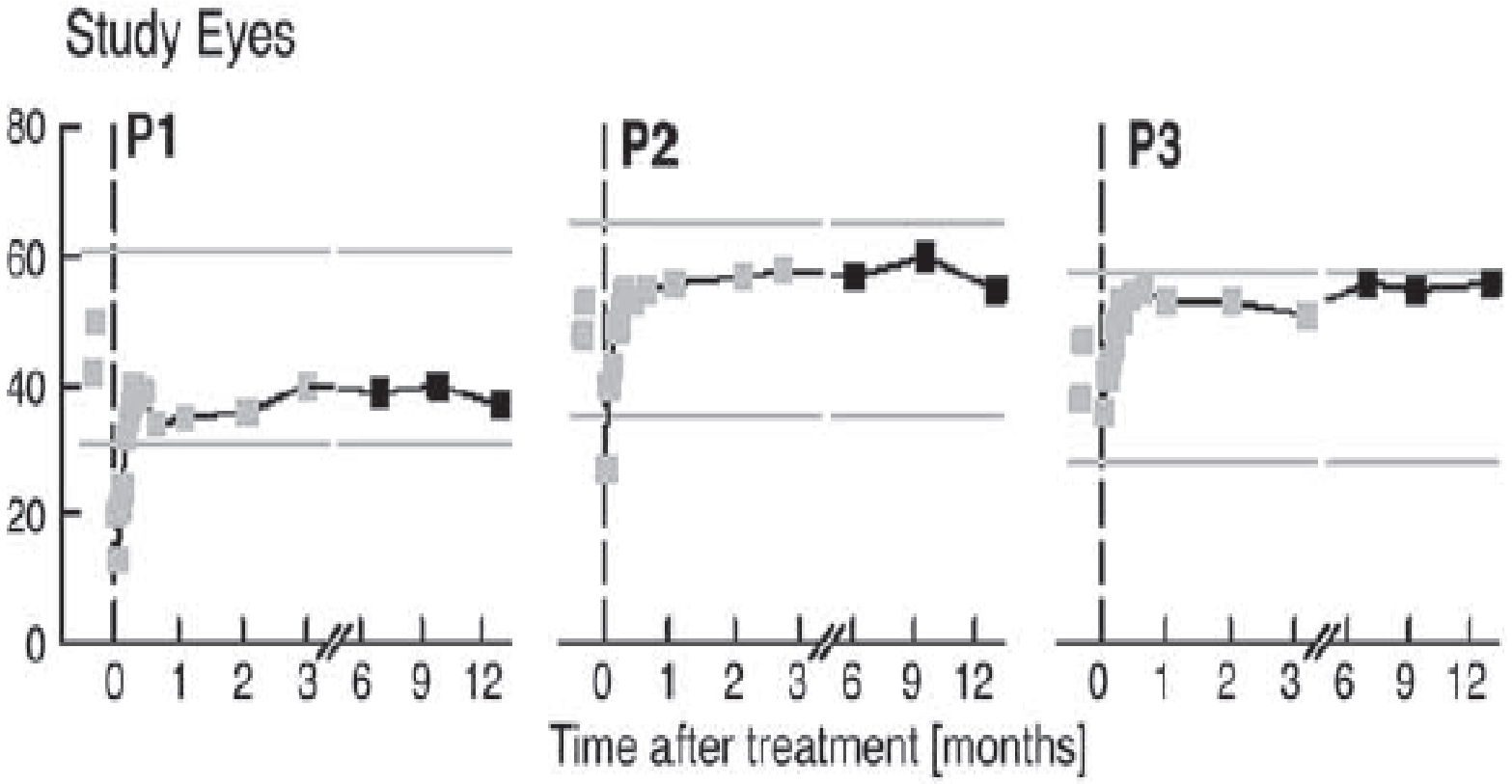
Visual Acuity (# of Letters) Following Gene Therapy for Leber Congenital Amaurosis



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

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