Clinical Studies in Enzyme Deficiency Disorders

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Outline

• Enzyme deficiency diseases historical perspective
• Drug development considerations
• Examples
  – Taliglucerase
  – Carglumic acid
  – Icatibant
• Key points
Regulatory Experience & Enzyme Deficiency Disorders

• Active area of drug development -- and approvals\(^1\)
• Selected moments in orphan enzyme deficiency history

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Passage of Orphan Drug Act</td>
</tr>
<tr>
<td>1983</td>
<td>Hemin</td>
</tr>
<tr>
<td>1986</td>
<td>Na+benzoate Na+phenylacetate</td>
</tr>
<tr>
<td>1987</td>
<td>(\alpha)-1-antitrypsin</td>
</tr>
<tr>
<td>1990</td>
<td>Factor IX</td>
</tr>
<tr>
<td>1990</td>
<td>pegadamase</td>
</tr>
<tr>
<td>1991</td>
<td>alglucerase</td>
</tr>
<tr>
<td>1990s-2000s+</td>
<td>numerous LSD ERTs</td>
</tr>
<tr>
<td>1996</td>
<td>betaine</td>
</tr>
<tr>
<td>2002</td>
<td>nitisinone</td>
</tr>
<tr>
<td>2003</td>
<td>miglustat</td>
</tr>
<tr>
<td>2007</td>
<td>sapropterin</td>
</tr>
</tbody>
</table>

\(^1\)Talele SS et al. Therapies for inborn errors of metabolism: What has the orphan drug act delivered? Pediatrics 201;126:101-106
Enzyme Deficiency Disorders

• Highly diverse:
  – Collection of disorders, e.g.
    • Amino acid metabolism, lysosomal storage disorders, coagulation factors, and others
  – Disease manifestations, e.g.
    • Multi-system vs. limited disease or target major morbidity
  – Strategies, targets, e.g.

<table>
<thead>
<tr>
<th>Replace enzyme</th>
<th>Enhance residual enzyme activity</th>
<th>Alter gene transcription</th>
</tr>
</thead>
</table>
| -enzyme replacement therapy 
-enzyme therapy 
-stem cell transplantation 
-organ transplantation 
-delivery to “inaccessible” compartments | -chaperones 
-co-factors | -e.g., anti-sense RNAs |

<table>
<thead>
<tr>
<th>Target substrate/substrate production</th>
<th>Target products</th>
<th>Target clinical outcome</th>
</tr>
</thead>
</table>
| -subrate reduction therapy 
-target upstream pathway 
-exploit alternate pathways 
-enzyme substitution | -exploit alternate pathways 
-downstream pathways 
-non-specific reduction of toxic catabolites | -enhance function 
-ameliorate disease manifestations |
Drug Development Considerations

• Diverse diseases, outcomes, and products necessitate different approaches to drug development

• For marketing approval:
  – Demonstrate “substantial evidence”\(^2\) of efficacy, safety and quality
    • Efficacy $\rightarrow$ clinically meaningful benefit/outcome
      – Impact upon how a patient feels, functions or survives
    • Favorable benefit-risk
  – Or Accelerated Approval based on:
    • Surrogate endpoint reasonably likely to predict clinical benefit, or
    • Clinical endpoint other than survival or irreversible morbidity
    • Subject to requirement for further study to verify clinical benefit in the post-marketing period

\(^2\)PHS Act 505(d)
Substantial Evidence

• For both pathways, efficacy evidence from adequate and well-controlled (A&WC) trials:
  “on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use”

• A&WC = Trial has been designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation”

• Regulations allow for “flexibility” and “scientific judgment” in how this is achieved
  - E.g., ~2/3 of rare disease marketing approvals rely upon one A&WC trial + supporting evidence (usual standard is 2)
  - Considerable diversity in study designs, endpoints, etc.

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2 PHS Act 505(d)  321CFR §314.126, Adequate and well-controlled studies.
421CFR §314.105 Approval of an application and an abbreviated application
Examples

• Recent enzyme deficiency disorder product approvals in CDER
  - Taliglucerase (Elelyso)\textsuperscript{7} for treatment of Gaucher disease type 1, an LSD (2012)
  - Icatabant (Firazyrr)\textsuperscript{8} for treatment of hereditary angioedema (HAE) (2011)
  - Carglumic acid (Carbaglu)\textsuperscript{9} for treatment of N-acetylglutamate synthase (NAGS) deficiency, an urea cycle disorder (UCD) (2010)

Drugs@FDA, Label and Approval History. Elelyso (taliglucerase alfa),\textsuperscript{7} Firazyrr (icatibant acetate),\textsuperscript{8} Carbaglu (carglumic acid).\textsuperscript{9} Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name
Taliglucerase

• Gaucher disease type 1
  – Glucocerebrosidase deficiency leading to glucocerebroside accumulation in cells t/o body, especially spleen, liver, bone marrow
  – Prevalence ~1/50,000-100,000 in US
  – Hepatosplenomegaly, anemia, ↓platelets, bone disease

• 4th enzyme and 5th approved product to treatment Gaucher disease type 1. Prior approvals based-on:

<table>
<thead>
<tr>
<th>Product</th>
<th>Major Endpoints in Efficacy Trials</th>
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<tbody>
<tr>
<td>Alglucerase&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Δ liver and spleen volume, Δ hgb and plt counts</td>
</tr>
<tr>
<td>Imiglucerase&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Δ liver and spleen volume, Δ hgb and plt counts</td>
</tr>
<tr>
<td>Miglustat&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Δ liver and spleen volume, Δ hgb and plt counts</td>
</tr>
<tr>
<td>Velaglucerase&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Δ liver and spleen volume, Δ hgb and plt counts</td>
</tr>
</tbody>
</table>

<sup>12</sup>Zavesca (miglustat) Package Insert 2010
<sup>13</sup>Elelyso (taliglucerase alfa) Full Prescribing Information 2012
Taliglucerase Development Program

• Efficacy and safety assessed in one trial
  – Study 1: DB, R (to dose), 2-dose cohort study in 31 adult tx-naïve patients X 9 months
  – Results\textsuperscript{14}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Δ from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tali 30 U/kg, n=15</td>
</tr>
<tr>
<td>Spleen volume (% BW) MN</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>-4.5</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>1.6</td>
</tr>
<tr>
<td>Liver volume (% BW)</td>
<td>-0.6</td>
</tr>
<tr>
<td>Plt (mm\textsuperscript{3})</td>
<td>11,427</td>
</tr>
</tbody>
</table>

MN = multiples of normal adjusted for body weight

– Supportive Study 2: OL, single-arm S&E in 25 patients on stable treatment with imiglucerase, switched over to taliglucerase
  • Spleen and liver volume, Hgb and plt were stable on average through 9 mos of treatment

Taliglucerase Key Points

• Clinical development program well-planned and based on existing body of knowledge
  - Natural history well understood
  - Prior, long-term history with similar products
    • Informed regulatory path and trial design
    • Existing long-term Gaucher patient registries
  - Objective, pharmacodynamic endpoints relevant to the disease and important clinical manifestations
  - Robust, statistically significant findings, large magnitude
    • Small efficacy trial
  - Relevant populations (tx-naïve, maintenance) included in development program to support labeling
Carglumic Acid

• NAGS deficiency, rarest of UCDs
  - Deficiency results in inability to metabolize amino acids
  - Prevalence ~50 patients worldwide, <10 in US
  - Hyperammonemia, recurrent neurologic crises resulting in progressive severe CNS impairment and premature death

• Prior to AP, 3 approved non-specific treatments for UCDs
  - Na+phenylbutyrate (Buphenyl)
  - Na+benzoate + Na+phenylacetate (Ammonul, Ucephan)

• Carglumic acid approved in EU~10 years earlier
Carglumic acid = synthetic structural analogue of NAG, an essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1)

Carglumic Acid Development Program

• Retrospective case series in 23 patients with NAGS deficiency treated over 16 years\textsuperscript{16}
  – 13 evaluable patients with “complete” documentation of ammonia levels and clinical course
  – 6 evaluable patients without concomitant ammonia lowering therapies or protein restriction

• Efficacy outcomes
  – Plasma ammonia, glutamine and citrulline levels in short and long term
  – Growth, neurological and psychomotor developmental outcomes

• No formal statistical analysis, historically controlled
  – Historical controls are one of the valid accepted controls
  – To be meaningful, require well-defined and well-understood disease histories

\textsuperscript{16}Carbaglu (carglumic acid) Drugs@FDA, Label and Approval History. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name
# Efficacy Evaluation: Plasma Ammonia

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Short-term (Day 1)</th>
<th>Short-term (Day 2)</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>270.8 (358.8)</td>
<td>180.7 (357.7)</td>
<td>68.5 (78.0)</td>
<td>23.0 (6.89)</td>
</tr>
<tr>
<td>Median</td>
<td>157.0</td>
<td>64.5</td>
<td>44.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Range</td>
<td>72.0-1428.0</td>
<td>25.0-1190.0</td>
<td>11.0-255.0</td>
<td>9.0-34.0</td>
</tr>
</tbody>
</table>

- Long-term treatment:  Median 5.8 years; range 1.3-16 years
- All patients demonstrated consistent and sustained lowering of plasma ammonia levels
- All were treated exclusively with carglumic acid in the long-term
- Some of these patients were treated initially with other ammonia lowering therapies
Efficacy Evaluation: Neurologic Outcome

23 patients in case series

3 missing data and 3 heterozygotes excluded

17 patients

3 normal baseline

3 (16%) remained normal

14 abnormal baseline

9 (53%) improved

5 (29%) remained abnormal
Icatibant

• HAE
  - Deficiency of the C1 esterase inhibitor,
    • Protein of the complement system
    • Affects 1 in 10,000-50,000 individuals worldwide
  - Unpredictable recurrent attacks of angioedema (swelling of face, extremities, GI tract and upper airways), abdominal pain, vomiting, laryngeal edema
  - 3rd product approved for treatment of acute attacks of HAE
    • Plasma-derived C1 inhibitor (Bertinert)
    • Ecallantide (Kalbitor), a kallikrein inhibitor
Icatibant Development Program

• Three efficacy trials – largely similar in design
  – Study 1: R, DB, PC trial in 64 patients
  – Study 2: R, DB, active-controlled (vs. tranexamic acid) trial in 77 patients
  – Study 3: R, DB, PC trial in 98 patients
  – OL, long-term extension study to all 3 trials

• For Study 3
  – New Patient Reported Outcome (PRO) development for the efficacy trials
    • 3-symptom Visual Analog Scale for a skin swelling, skin pain, abdominal pain (VAS-3)
      – Responder defined as >50% reduction in 3-symptom composite VAS (abd pain, skin pain, skin swelling) sustained over 3 consecutive timepoints
    • PRO supported by conduct of an observational, non-interventional study in 80 adult HAE patients, patient debriefing interviews, literature review, and expert opinion
      – Primary endpoint time to onset of symptom relief in VAS-3

Icatibant Results

• Study 3: Time to onset of symptom relief based on VAS-3

- Median time to 50% reduction in symptoms was 2 hours in icatibant group vs. 19.8 hours in placebo group

Development Program Highlights

• Enzyme deficiency disorders characterized by substantial diversity (both between and within diseases)
  - E.g., chronic progressive vs. episodic, time course
  - Organ systems affected
  - Symptomatic assessment vs. objective measurements (e.g., biomarkers)

• Interventions are also diverse
  - Biologics vs. drugs
  - ERT vs. co-factor replacement
  - Expected time course of intervention/measureable results

• Study designs considerably different
  - what makes sense for the disease, drug and expected outcomes
Key Point #1: Keep Goals in Mind

- We all want the same thing
  - Effective drugs with favorable benefit-risk
  - Based on substantial evidence of effectiveness, safety and quality
  - Efficient clinical development programs
  - Correct public health decisions
Key Point #2: Getting to Goal

• A&WC trials designed from understanding of disease, drug’s expected effects, population under study, how effects will be measured and over what period of time, among other things
  – Study designs will vary
• Scientific foundation, knowledge base are critical to success
  – Disease natural history
  – Pathophysiology
  – Drug’s MOA
  – Regulatory experience, prior knowledge with related products or similar diseases, and pilot studies with the investigational agent
  – Endpoint development/outcome assessments
    • May need lead-time for development
• For rare diseases, there is a limited opportunity for study and replication
  – Careful planning is essential
  – Maximize all opportunities for learning