Natural History Studies for Drug Development

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- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies

Overview

- Rare disease definition
- Challenges in rare disease drug development
- Natural history and clinical development
- Examples of drug approvals using natural history data

Background

- Rare disease definition:
  - affects less than 200,000 people in the United States
- ~ 7,000 recognized rare diseases
- Most rare diseases have no approved therapies
- Highly heterogenous group of disorders with high phenotypic diversity within individual disorders

Challenges of Rare Disease Drug Development

- Phenotypic heterogeneity
- Small number of disease-affected individuals
- Conduct trials in pediatric populations
- Lack of understanding of the natural history of the disease
- Leading to difficulty in development of an adequate and well-controlled study

Natural History of a Disease

- Traditionally defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease onset until either the disease resolution or the individual's death

Natural History Study

- Retrospective and/or prospective observational study
- Intended to track the course of the disease.
- Identify demographic, genetic, environmental, and other variables that correlate with the disease's development and outcomes.

Designing a Natural History Study

- **Prospective vs Retrospective**
  - Prospective studies preferable due to less bias, newer biomarkers (potentially more relevant information), similar standard of care

- **Cross-sectional vs Longitudinal**
  - Longitudinal studies provide more comprehensive information regarding disease onset and progression over time

Natural History Study Contribution to the Clinical Development Program

1. Identification of the patient population
2. Identification or development of clinical outcome assessments
3. Identification or development of biomarkers
4. Design of externally controlled studies

Identification of the Patient Population

- Uncover sentinel events or detectable physiologic changes that are important predictors of disease progression or that are clinically important
- Identify specific patient subgroup(s) that may be benefit from a particular drug trial
- Can be used to decide the inclusion criteria, stage of disease to treat, duration of a trial, frequency of data collection, specific endpoints

Identification or Development of Clinical Outcome Assessments (COA)

- Evaluate the ability of a new or existing COA to detect change in a particular disease or a pattern of progression in a disease
- Also can be used to evaluate the performance and reproducibility of a COA for a clinical investigation
- COA used in trials to assess efficacy and safety of drug

Identification or Development of Biomarkers

- Biomarker: indicator of normal biological processes, pathologic processes, or biological responses to a therapeutic intervention
- Identify biomarkers that:
  - Diagnose the disease
  - Predict the disease's course
  - Predict a treatment response
  - Guide patient selection
  - Guide dose selection in drug development programs

Design of Externally Controlled Studies

- FDA regulations recognize historical controls as a possible control group
- Requires very careful planning and assessment

Comparability Issues with External Controls

- Patient demographics
- Diagnostic criteria
- Stage or severity of disease
- Concomitant treatments
  - Standard of care differences
- Observational conditions
  - Methods of assessing outcome

Rare Disease Approval Using Natural History Data

- Brineura
- Crysvita

Brineura (cereliponase alfa)

- Recombinant human tripeptidyl peptidase-1
- Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile CLN2
- Intraventricular administration into the cerebrospinal fluid by infusion via a surgically implanted reservoir and catheter

Brineura Clinical Program

- Interventional trial:
  - single arm, open label for 48 weeks with extension
  - 24 patients
  - efficacy: modified CLN2 motor and language scale
- Natural history study:
  - European registry (42 patients)
  - retrospective medical information and parental interview with a small prospective observational period
  - efficacy: original CLN2 motor and language scale

Review Challenge

- Differences in baseline demographics between the historical control and treatment group (gender, age, genotype)
- Different versions of the clinical reported outcome were used between the two cohorts
- Inconclusive efficacy results after 48 weeks of treatment

Outcome

- Efficacy was based on best matched patients in the two cohorts, accounting for several confounding factors (age, genotype, baseline motor score)
- Efficacy was focused on the motor domain and not the language domain due to lack of comparability
- Efficacy was evaluated at 96 weeks

Crysvita (burosumab)

- Fibroblast growth factor 23 (FGF23) blocking antibody

- Treatment of x-linked hypophosphatemia in adult and pediatric patients 1 year of age and older

Crysvita Pediatric Clinical Program

- Interventional trial:
  - single-arm, open label trial
  - 52 patients
  - primary efficacy: rickets by x-ray

- Natural history study:
  - retrospective
  - 52 patients
  - efficacy: rickets by x-ray

Review Challenge/Outcome

- Challenge:
  - differences in baseline demographics (age, baseline level of rickets)

- Outcome:
  - x-ray pairs were matched
  - x-rays were de-identified, intermixed with the treatment group and read by the same radiologists

Key Points

- Natural history studies can provide the scientific foundation upon which a drug development program can be built

- Natural history study data can be more informative in the pre-IND phase to help design of the efficacy trials

- Need to be able to control for bias and ensure comparability when considering a natural history study as an external control.


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