AN INDUSTRY PERSPECTIVE ON THE USE OF RWE FOR REGULATORY PURPOSES: EXPERIENCE FROM RARE DISEASES

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• Opinions and views expressed here today are my personal views and do not represent Takeda’s collective view or position, nor do they express the views, position or opinions of other industry stakeholders.

• Full time employee of Takeda Pharmaceuticals and shareholder.
WHAT IS THE DEFINITION OF A RARE DISEASE? HOW RARE IS RARE?

- United States FDA definition of rare disease\(^1\):
  - Affects < 200,000 persons in the United States
  - Affects > 200,000 persons but the costs will not be recovered for developing product

- EU definition of rare disease\(^2\):
  - < 5 per 10,000

- There are > 6,000 rare diseases\(^2\)

\(^1\)FDA. Developing products for rare diseases and conditions. Available at: [https://www.fda.gov/industry/developing-products-rare-diseases-conditions](https://www.fda.gov/industry/developing-products-rare-diseases-conditions). Accessed on: April, 2019

A FEW EXAMPLES OF RARE DISEASE

Duchenne Muscular Dystrophy
Hereditary Angioedema
Hemophilia
Congenital Protein C Deficiency
Hunter Syndrome
Primary Immune Deficiency

~0.62:100,000 male births\(^2\)

\(\sim 2:100,000\) persons\(^1\)


CHALLENGES IN DEVELOPING THERAPEUTICS FOR RARE DISEASE: CURRENT EXPERIENCE AND OPPORTUNITIES FOR USE OF REAL WORLD EVIDENCE (RWE)

- Natural history of disease often not well characterized
- Potentially not feasible/unethical to conduct randomized placebo controlled study
- Challenging to evaluate effectiveness in special populations
- Rare diseases often have a long diagnostic journey and frequently it is difficult to enroll patients in trials

Note: Presenter’s own perspective/experience
NATURAL HISTORY STUDIES USING REAL WORLD DATA CAN PROVIDE IMPORTANT INFORMATION ON CLINICAL COURSE OF DISEASE

- Disease progression
- Burden of illness
- Standard of care
- Background rates of comorbid conditions
- Outcomes that are important to the patient, including patient reported outcomes (PROs)

REGISTRIES PROVIDE SOURCE OF DATA FOR NATURAL HISTORY STUDY

• **Icatibant Outcome Survey (IOS)**¹
  - Initiated in 2009 as part of a commitment to regulatory authorities
  - HAE I/II patients enrolled ➔ Initially icatibant only patients but expanded to include patients on C1-esterase inhibitors
  - In addition to data collected from normal clinical practice, IOS also collects data on HAE attacks, an important clinical outcome that is not captured with regularity in existing medical records
  - Provides context to newer clinical trial data on the progression of HAE disease

• **Hunter Outcome Survey (HOS)**²
  - Initiated in 2005 as part of a commitment to regulatory authorities
  - MPS II patients enrolled
  - In addition to data collected from normal clinical practice, patients also were able to complete a Patient Reported Outcome (HS-FOCUS)*
  - Provides context to newer clinical trial data on progression of Hunter Syndrome

*HS-FOCUS: Hunter Syndrome - Functional Outcomes for Clinical Understanding Scale

HAE: Hereditary Angioedema
MPS II: Mucopolysaccharidosis type II

LONGITUDINAL COHORT DATA IN PARALLEL TO CLINICAL TRIAL ADDS CONTEXT TO TRIAL DATA

• Hunter Syndrome longitudinal cohort study conducted in parallel to clinical trial

• Patients aged 2-18 years of age with a concomitant medication for Mucopolysaccharidosis type II enrolled (N=55)

• Measured the same Patient Reported Outcomes (PRO) as the clinical trial: Differential Abilities Scales®, second edition (DAS-II) and Vineland Adaptive Behavior Scales™, second addition (VABS-II)
  – Association with the HS-FOCUS that was also collected (PRO used in natural history study)

• Evaluated changes in PRO measurements over time

1Yee et al. Analysis of cognitive ability and adaptive behavior assessment tools used in an observational study of patients with Hunter syndrome. 15th Annual WORLD Symposium™, February 4–8, 2019, Orlando, FL, USA
CHALLENGES IN DEVELOPING A REGISTRY OR A PROSPECTIVE OBSERVATIONAL STUDY FOR REGULATORY PURPOSES

• **Critical data elements**: which elements are able to be collected reliably, are important to patients, and will be relevant data elements to provide context to ongoing clinical trials

• **Timing of registry**: must start early enough in development to have enough data and not compete with developmental studies

• **Geographical representation**: Some countries/sites may have very few patients, if conducting prospective observational study at same time, patient recruitment becomes difficult

• **Disease registry (vs. product only registry)**: The optimal type of registry is a disease registry, however, this can be challenging in a competitive landscape

• **Comparison of patients**: patients enrolled in trials are likely to be very different (especially if enrolled concurrently); historical controls may also not be similar due to changes in standard of care

Note: Challenges are identified from presenter’s own perspective/experience
HISTORICAL CONTROLS HAVE BEEN USED FOR REGULATORY APPROVAL IN RARE DISEASE/CANCER

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hypoammonemia/severe urea cycle disorders</td>
<td>sodium phenylacetate and sodium benzoate</td>
<td>2005</td>
</tr>
<tr>
<td>Pompe Disease (alpha-glucosidase deficiency)</td>
<td>algucosidase alfa</td>
<td>2006</td>
</tr>
<tr>
<td>Toxic plasma methotrexate concentrations</td>
<td>glucarpidase</td>
<td>2012</td>
</tr>
<tr>
<td>Relapsed or refractory Acute Lymphoblastic Leukemia (ALL)</td>
<td>blinatumomab</td>
<td>2014</td>
</tr>
<tr>
<td>Hypophosphatasia (HPP)</td>
<td>asfotase alfa</td>
<td>2015</td>
</tr>
<tr>
<td>Lysosomal acid lipase (LAL) deficiency</td>
<td>sebelipase alfa</td>
<td>2015</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis type 2 (CLN2 disease)</td>
<td>Cerliponase alfa</td>
<td>2017</td>
</tr>
</tbody>
</table>

For the majority of these examples, statistical approaches were not used to compare the single-arm intervention to the historical control. Propensity score approaches were used for blinatumomab historical control comparison.

1Lim et al. Minimizing patient burden through the use of historical control data in innovative confirmatory trials: review of methods and opportunities. Therapeutic innovation and regulatory science 2018, Vol. 52 (5)546-559.
Eculizumab pediatric indication for atypical Hemolytic Uremic Syndrome (aHUS)¹

- Retrospective registry data of 19 pediatric patients (<18 years of age) supplemented formal clinical trial in this sub-population
- Clinical outcomes were nominally compared to pivotal trials, no formal analyses conducted

Extension of eculizumab indication in the EU to patients without history of transfusion²

- Global Paroxysmal Nocturnal Hemoglobinuria (PNH) registry was approved to be used in place of a randomized controlled trial to expand indication


Patients with rare diseases have a long diagnostic journey and a high misdiagnosis rate\(^1\).

It is often difficult to identify patients for inclusion in clinical trials; a situation not uncommon with most rare diseases or select subgroups\(^1\).

New methodologies that leverage: electronic medical records, administrative claims, registries, and chart reviews would increase efficiencies of clinical trials and would be able to\(^2\):

- Improve identification of patients for clinical trials
- Confirm surrogate, physician-reported, Patient Reported Outcomes (PROs) and other alternative endpoints from clinical trials
- Perform comparative effectiveness studies using linked PROs as co-primary or secondary endpoints


\(^2\)Presenter’s own perspective/experience
Of 130 confirmed cases, 65% were identified through administrative claims and EMR. Such methodology can be used to refine clinical definitions and risk factors which may result in earlier diagnosis and treatment and identification for clinical trials.

FINAL THOUGHTS

• Real world evidence is used for drug development and regulatory purposes in the rare disease space

• Experience from the study of rare diseases can provide insight for the use of real-world evidence in other therapeutic areas

• Many opportunities for methodologic development in order to insure robust data for regulatory evaluation

Note: Presenter’s own perspective