Introduction: Challenges to generate Real-world Evidence (RWE) in Rare Diseases

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Disclosure statement

D Rosenberg is an employee of Actelion Pharmaceuticals Ltd, **Johnson and Johnson.**

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300

6000+

70%

5%

72%

RareDiseaseDay.Org

A window into a rare disease, Niemann-Pick disease Type C

Orphanet J Rare Dis. 2020; 15: 104.
Published online 2020 Apr 25. doi: 10.1186/s13023-020-01363-2
PMCID: PMC7183679
PMID: 32334605

Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: a final report of the NPC Registry

Received: 23 January 2020 | Revised: 20 March 2020 | Accepted: 17 April 2020
DOI: 10.1002/jimd.12245

ORIGINAL ARTICLE

JIMD SSIEM

Long-term survival outcomes of patients with Niemann-Pick disease type C receiving miglustat treatment: A large retrospective observational study

Regulatory agencies' outlook

- An orphan drug is a drug intended for use in a rare disease.

- Varied definitions
  - World Health Organization defines a rare disease—sometimes referred to as an orphan disease—as one that affects fewer than 65 per 100,000 people.
  - United States - FDA, a rare disease is one that affects fewer than 200,000 people.
  - EU – EMA defines an orphan disease as one that affects no more than 5 per 10,000 individuals.
- To-date
  - From 2003-2023, > 2870 medicines with EMA orphan designation, and over 240 orphan medicines authorised in the EU.
  - From ODA (1983) to 2023, 6340 orphan drug designations passed covering 1079 rare diseases.
    - 882 of the ODD resulted in at least one approval for use in 392 diseases, 5-10% of all rare diseases.

Fermaglich et al. 2023; https://www.ema.europa.eu/en/documents/leaflet/infographic-orphan-medicines-eu_en.pdf

Solutions and Challenges (1/3)

Rare Disease needs	Solutions	Methods challenge
Little known on epidemiology, natural history and burden of diseases	– Secondary use data sources such as EHR/insurance claims may offer large sample sizes. Population-level data can support calculations of incidence, prevalence, survival – Registries/clinical cohorts may offer deep clinical detail and natural history follow-up for complex medical conditions	- Identifying the disease (phenotype/classification systems) - Denominators, projection when data are not population-level - Limited follow-up (vs. registry) in large administrative data sources or linkage possibility for key outcomes of interest
Small, heterogenous, populations	- Large secondary use data sources may provide more patients - Registries can gather patients from scattered geography and specialist centers - Pooling secondary use of data (large admin and/or registries) across (federated) networks can increase sample size and can bring together geographically isolated / scattered groups of or single patients	– May be selection biases / generalizability issues. – Low patient count and valid treatment comparator may be unavailable for comparative effectiveness / safety outcomes (self-controlled designs help but have limitations) – Methodological complications to control confounding – Multiple governance and analytical issues with (federated) data networks

Solutions and Challenges (2/3)

Rare Disease needs	Solutions	Methods challenge
Delays in diagnosis, from early symptoms to diagnosis and beyond	- Secondary use RWD sources such as large EHR/Claims with data before diagnosis helps identify order and timing of symptoms and can quantify diagnosis delay - EHRs/digital health tracker/tests/images data before diagnosis helps develop prediction models for identify patients who have rare disease earlier	- Identifying the symptoms/ disease (phenotype/classification systems) - Duration of look-back to identify patient journey - Positive predictive value of prediction models in small populations

Solutions and Challenges (3/3)

Rare Disease needs	Solutions	Methods challenge
Inform RD Trial or act as comparator	– Data from secondary use databases can improve statistical efficiency of trial or be used for comparators (external controls)/ de novo data collection for RWD control – Validate surrogate endpoints	– Be clear on intended use of RWE – Study design considerations, different follow up methods – Varied recruitment strategies between trial and RWD source
RWD sources: Quality and quantity	– Consider broad array of RWD, registries, claims, EHRs, patient generated, other	– Determine, plan and document clearly the data quality processes – Linkage with other data sources – Be clear on original intended use of RWD as can lead to missingness/bias – data quality may result in information bias

Thank You and Acknowledgements

Rare Disease Patients

Global Epidemiology, J&J

Rare Disease Community of Practice, J&J

ISPE Rare Diseases SIG

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