NAVIGATING THE CHALLENGES OF CLINICAL DEVELOPMENT IN RARE DISEASES : LESSONS LEARNED AND HURDLES TO OVERCOME

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RARE DISEASE: DEFINITIONS

Core definition (WHO)

A rare disease is a medical condition with a specific pattern of clinical signs, symptoms, and findings that **affects fewer than or equal to 1 in 2000 persons** living in any World Health Organisation-defined region* of the world.

*WHO-defined regions are: Africa, Americas, Eastern Mediterranean, Europe, South-east Asia, Western Pacific

REGULATORY DEFINITIONS

Regulating Agency	Prevalence Threshold	Source
US-FDA	<200.000	Orphan drug act, 1983
EU-EMA	5 in 10.000	EC 141/2000
Japan-PMDA	<50.000	JPMA, 2008

While the frequency of most rare diseases is characterized by **prevalence** some rare diseases, such as rare cancers and rare infectious diseases, can be more precisely described by **incidence** .

ULTRA-RARE DISEASE DEFINITIONS

An **ultra-rare disease** is a rare disease that affects an extremely small number of people worldwide.

- There is no universally accepted definition of an ultra-rare disease.
- Some common definitions include:
- Affecting fewer than 1 in 50,000 people globally
- Affecting fewer than 1 in 10,000 people in a specific country or region
- Having a prevalence of less than 1 per million people

RARE DISEASE, BUT SIGNIFICANT BURDEN

- Over 7000 rare diseases are currently defined
- Over 300 million people worldwide (between 3-8% of population) live with rare diseases
- Around 80% of rare diseases have a genetic cause
- Almost 70% of which present in childhood \
- About 95% lack approved treatments
- The average time for an accurate diagnosis is 4·8 years;
- About 30% of children with a rare disease die before age 5 years.
- The National Economic Burden of Rare Disease Study in the US estimated the economic cost of 379 rare diseases reached nearly **$1 trillion** in the U.S. in 2019 in direct medical and indirect non-medical cost.

Nguengang Wakap S et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020 Feb;28(2):165–73.

1.The landscape for rare diseases in 2024

The Lancet Global Health, Volume 12, Issue 3, e341

FROM URGENCY TO COMPLEXITY: THE ROAD TO RARE DISEASE THERAPIES

Developing therapies for rare diseases is critically important given the scale of unmet need

However, the path from concept to approval is complex and often challenging

CURATIVE VS. DISEASE-MODIFYING THERAPIES IN RARE DISEASES

Curative therapies

- Aim to eliminate the underlying cause of the disease
- **Examples:** Gene replacement in monogenic disorders
- Often delivered as a one-time intervention (e.g., gene therapy)
- Require long-term follow-up to assess durability and safety

Disease-modifying therapies

- Do not cure but aim to slow progression, alleviate symptoms, or improve quality of life
- Often used in polygenic or poorly understood conditions
- May require chronic administration
- **Examples:** Small molecules, biologics, RNA-targeting therapies

COMPLEXITIES OF DEVELOPING GENE THERAPIES IN RARE DISEASES

	Category	Key Challenge Summary
🧬	Target & Vector Design	Requires deep knowledge of gene function; vector selection impacts delivery & safety
🏭	Manufacturing	High cost, long lead times, scale-up difficulties, batch variability
🧪	Preclinical Models	Often no suitable animal model; safety data limited
👩‍⚕️	Clinical Trial Design	Small N; need for adaptive/single-arm trials; long-term monitoring
📋	Regulatory Considerations	Evolving guidelines; extensive post-marketing commitments
⚖️	Ethical & Access Issues	Informed consent in pediatrics; access barriers; high upfront therapy costs

CHALLENGES IN RARE DISEASE THERAPY DEVELOPMENT – SPONSOR PERSPECTIVE

- Scientific & Regulatory
- Logistical
- Economic
- Ethical

SCIENTIFIC & REGULATORY CHALLENGES

- Limited understanding of disease biology
- Scarce natural history data
- Progressive nature
- Phenotypic Variability

SCIENTIFIC & REGULATORY CHALLENGES

- Lack of validated biomarkers and endpoints and use of surrogate endpoint
- Evolving and region-specific regulatory requirements

LOGISTICAL CHALLENGES

- Small, geographically dispersed patient populations
- Limited number of specialized centers
- More satellite sites- higher variability, high cost
- Funnelling patients to a central site may be difficult for many patients and caregivers

ECONOMIC CHALLENGES

- High development costs with uncertain commercial return
- Reimbursement uncertainty
- Long-term post-marketing commitments
- Heavy reliance on incentives (e.g., Orphan Drug designations)

ETHICAL CHALLENGES

- Patients in low- and middle-income countries often excluded from trials
- In cases where they are included, therapies may never become available, affordable, or approved locally
- Equity concerns around access to life-saving therapies
- Informed consent challenges, pseudo-anonymization issue especially in the space of ultra-rare diseases

KEY **REGULATORY PATHWAYS** THAT SUPPORT FASTER AND MORE FLEXIBLE APPROVAL OF THERAPIES FOR RARE DISEASES: FDA

- **Orphan Drug Designation (ODD)**
  - Provides benefits such as 7 years of market exclusivity, tax credits, and waived FDA fees.
- **Fast Track Designation**
  - Designed to expedite the development of drugs for serious conditions with unmet medical needs.
  - Allows for more frequent interactions and rolling review of the NDA/BLA.
- **Breakthrough Therapy Designation**
  - For drugs showing preliminary clinical evidence of substantial improvement over existing therapies.
  - Offers intensive FDA guidance and organizational support for efficient development.

KEY **REGULATORY PATHWAYS** THAT SUPPORT FASTER AND MORE FLEXIBLE APPROVAL OF THERAPIES FOR RARE DISEASES: FDA (2)

- **Accelerated Approval**
  - Allows early approval based on surrogate or intermediate endpoints that are reasonably likely to predict clinical benefit.
  - Requires confirmatory post-marketing trials.
- **Priority Review**
  - Shortens FDA review time from 10 to 6 months for therapies that offer significant improvements in safety or efficacy.
- **Rare Pediatric Disease Priority Review Voucher**
  - Granted with approval of a drug for a rare pediatric disease; the voucher can be redeemed for a six-month expedited review of a future drug application, or it can be sold on the open market.

KEY **REGULATORY PATHWAYS** THAT SUPPORT FASTER AND MORE FLEXIBLE APPROVAL OF THERAPIES FOR RARE DISEASES: EMA

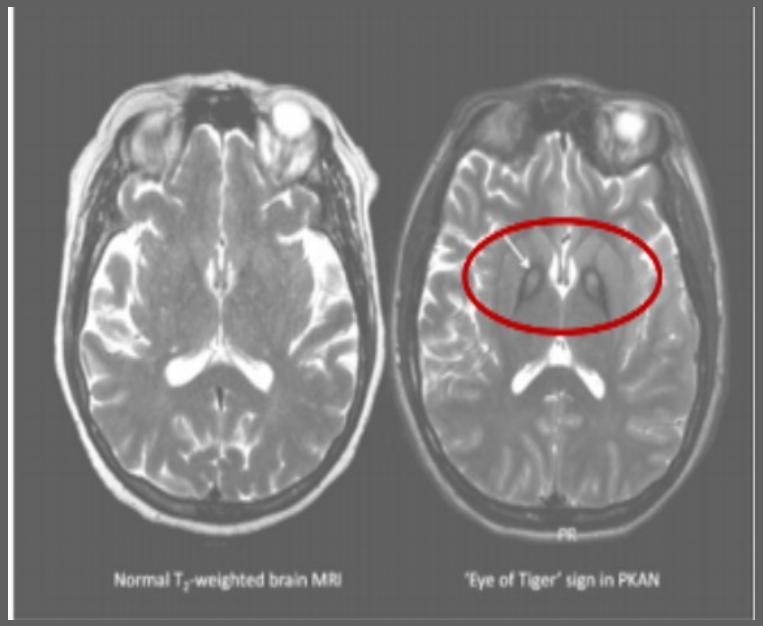
- **Orphan Medicinal Product Designation**
  - Provides 10 years of market exclusivity, protocol assistance, and fee reductions.
- **Priority Medicines (PRIME) Scheme**
  - For therapies addressing unmet medical needs based on early clinical data.
  - Offers enhanced early interaction to optimize development and speed up evaluation.
- **Accelerated Assessment**
  - Reduces 210-day assessment to 150 days for medicines of major public health interest.
- **Conditional Marketing Authorization**
  - Benefit of immediate availability outweighs the risk of less comprehensive data.
  - Requires further data post-approval to confirm benefit-risk balance.
- **Adaptive Pathways (Pilot)**
  - Flexible, iterative approach to evidence generation, particularly useful in small populations.
  - Involves early patient access, real-world data, and stepwise approvals.

REAL LIFE EXAMPLE: TIRCON

- TIRCON ("Treat Iron-Related Childhood-Onset Neurodegeneration) a research consortium funded by the EU
- Lasted from November 2011 until October 2015
- Comprised 13 partners from 8 countries
- TIRCON brought together the existing outstanding, but scattered expertise in NBIA research and care throughout Europe and internationally.
- Set-up a structured network to improve diagnosis and treatment of NBIA which persists beyond the project end.

REAL LIFE EXAMPLE: TIRCON STUDY

- Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic disorder characterised by progressive generalised dystonia and brain iron accumulation.
- Prevalence uncertain, but estimated to be anywhere between 1 in 1,000,000 to 3 in 1,000,000 individuals
- Deferiprone is an oral iron chelator, capable of penetrating blood blain barrier



REAL LIFE EXAMPLE: TIRCON STUDY

- 18-month, randomised, double-blind, placebo-controlled trial, followed by a pre-planned 18-month, open-label extension
- 4 sites: Germany, Italy, England, and the USA.
- Patients aged 4 years or older with a genetically confirmed diagnosis of PKAN
- Co-primary endpoints were the change from baseline to month 18 in the total score on the BAD scale (which measures severity of dystonia in eight body regions) and the score at month 18 on the PGI-I scale
- 100 patients screened, 88 randomized
- After 18 months, the BAD score worsened by a mean of 2·48 points in DFP group 3·99 points in Placebo group.
- No subjective change was detected by PGI-I scale
- Deferiprone was well tolerated, achieved target engagement (lowering of iron in the basal ganglia), and seemed to somewhat slow disease progression at 18 months, although not significantly, as assessed by the BAD scale.
- These findings were corroborated by the results of an additional 18 months of treatment in the extension study.
- The subjective PGI-I scale was largely unchanged during both study periods, indicating that might not be an adequate tool for assessment of disease progression in patients with PKAN.

Klopstock T, et al. Safety and efficacy of deferiprone for pantothenate kinase-associated neurodegeneration: a randomised, double-blind, controlled trial and an open-label extension study. Lancet Neurol. 2019 Jul;18(7):631-642. doi: 10.1016/S1474-4422(19)30142-5. PMID: 31202468.

REAL LIFE EXAMPLE: TIRCON STUDY (2)

Deferiprone trial results produce positive findings for some with PKAN

August 2019

The long-awaited results from the first international clinical trial for NBIA — testing deferiprone in individuals with PKAN — are in.

They show that the iron-chelating drug slowed the progression of the disorder in older patients with a later-onset, or atypical, form of PKAN, but did not have a similar benefit for younger patients with classic PKAN, which starts in early childhood.

In addition to those findings, the study showed that the drug successfully reduced the amount of accumulated iron in the brain for PKAN individuals, regardless of onset age.

PKAN, or Pantothenate Kinase-Associated Neurodegeneration, and all other NBIA disorders share iron accumulation in the globus pallidus structure of the brain. It remains unclear, however, whether excess iron causes NBIA or is brought on by some other problem.

The results of the trial, which was funded by a European Union grant titled Treat Iron-Related Childhood-Onset Neurodegeneration, or TIRCON, were presented at the Tenth International NBIA Family Conference held May 30 to June 2 in Charleston, S.C. The findings were then published in the July issue of the medical journal, Lancet Neurology.

The lead investigator of the trial in the United States, Dr. Elliott Vichinsky of the University of California, San Francisco Benioff Children's Hospital in Oakland, discussed the results at the conference. He said that older and younger PKAN individuals showed improvement with deferiprone in dystonia of the lower face and lower legs, as well as in cognitive functioning, especially memory. But the benefit in the younger children, who tend to have a faster-moving, more severe form of PKAN, "wasn't statistically significant," he said.

TIRCON STUDY LESSONS LEARNED

- Consortium made international and multifunctional collaboration possible
  - Increased disease awareness, diagnostics
- We piloted hybrid model funnelling patients to the 4 centers of excellence
  - There was a single US sites with patients from all over the country enrolled
  - Site in Germany service as a pivotal site for several EU countries
  - Some evaluations were conducted locally
- Active position of the NBIA community was major factor in successful recruitment
- Absence of a targeted evaluation scale made detection of the signal difficult
- Limited natural history data made interpretation of results difficult
- Co-Primary PGI-I carried significant recall bias over 18 months of therapy
  - This was the endpoint requested by the FDA.
- Use of concomitant therapies (Botox, DBA, baclophen) resulted in protocol deviations
- Evidence of efficacy was observed in atypical PKAN, suggesting potential benefit in this group
- However, due to missed primary endpoint the study did not lead to therapy approval

WAYS TO OPTIMIZE CLINICAL DEVELOPMENT IN RARE DISEASES

- **Multidisciplinary & Collaborative Approach**
  - Early involvement of clinical, regulatory, scientific, and operational experts
  - Partnerships with academic centers, CROs, and regulators
- **Flexible Regulatory Strategies**
  - Seeking early scientific advice and regulatory alignment and keep open continuous dialog
- **Patient-Centric Development**
  - Collaboration with advocacy groups for protocol input and recruitment
  - Get to know your patient population!

WAYS TO OPTIMIZE CLINICAL DEVELOPMENT IN RARE DISEASES

- **Leverage Innovation & Technology**
  - Use of omics, AI, and modeling to identify targets and endpoints
  - Integrating real-world data and natural history studies
- **Smart & Adaptive Trial Designs**
  - Exploring basket, platform, and adaptive designs
  - Using modeling and simulation for dose and endpoint optimization
  - Developing tailored and validated outcome measures
- **Hybrid & Decentralized Models**
  - Combine in-person and remote visits to boost access
  - Use telehealth, eConsent, and home health services
  - Maintain data integrity with centralized oversight
- **Global Consortia & Data Sharing**
  - Active participation in rare disease networks and research consortia
  - Sharing registries and natural history databases
  - Pre-competitive collaboration

RARE DISEASE AWARENESS DAY

Rare disease awareness day- last day of February (28th or 29th February)- the day we wear stripes!

THANK YOU!