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Orphan Drugs and Rare Diseases - A Review

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ABSTRACT

As the incidence of rare diseases increases each year, the total number of rare disease patients worldwide is nearly 400 million. An orphan drug can be defined as one that is used to treat an orphan disease. For example, haem arginate, used to treat acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, is an orphan drug. Industry has historically concentrated on small-molecule drugs, but developments in molecular biology and our understanding of the human genome have expanded our toolkit for drug discovery. A clinical orphan drugs, however, are rare and patients often struggle to utilize them and expensive medications during treatment. Orphan drugs have been the focus of new drug research and development for both domestic and international pharmaceutical companies as a result of the substantial investment being made in the field of rare diseases. Patients with these conditions often face significant medical, social, and economic burdens, and the development of orphan drugs represents a critical step in addressing their unmet medical needs. Clinical breakthroughs have been made in every field, from traditional antibodies and small molecule drugs to gene therapy, stem cell therapy and small molecules.

Key words: *Orphan drugs, coproporphyria, antibodies.*

INTRODUCTION

The term "orphan drug" refers to a pharmaceutical agent developed to treat a rare medical condition or disease, often referred to as an orphan disease. Orphan diseases are those that affect a relatively small number of people, making them less attractive for pharmaceutical companies to invest in due to limited potential for profit. The lack of financial incentive can lead to the abandonment or discontinuation of research and development for treatments of rare diseases. This phenomenon is often described as drugs being "orphaned" when companies decide to halt their efforts due to economic reasons. The Orphan Drug Act, as mentioned earlier, was established to address this issue by providing incentives to encourage the development of drugs for rare diseases and to ensure that patients with rare conditions have access to necessary treatments.

An orphan drug is typically defined as a medication used to treat a rare or orphan disease. For instance, haem arginate, employed in treating acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria is classified as an orphan drug. Interestingly, ibuprofen also falls under the category of an orphan drug, as it has been utilized in the treatment of an orphan disease-specifically, patent ductus arteriosus in neonates, regardless of whether they are orphans. This observation underscores the fact that obstacles to the development of orphan drugs are not limited to the premarketing stage. In some instances, it may not be commercially viable to conduct an efficacy trial, even for a drug with established efficacy in other contexts. Indeed, there might be little motivation to undertake an efficacy trial for a well-established drug in a rare condition or even in a relatively common condition

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affecting a subgroup of individuals-consider the numerous drugs licensed for use in adults but not in children.

Global Perspectives and Challenges

Over the past two decades, initiatives have emerged to encourage pharmaceutical companies to invest in the development of orphan drugs. The Orphan Drug Act, initially implemented in the USA in 1983 and mirrored by comparable legislation in Japan, Australia, and the European Community, marked a pivotal step in this direction. Strategies to stimulate orphan drug development include tax credits, research aids, streamlined marketing authorization procedures, and extended market exclusivity. However, in Europe, the focus on market exclusivity raises concerns about the need for additional incentives, particularly to ensure cost-effectiveness. If we define an orphan drug as one used to treat a rare disease, a rare disease could be characterized as one for which treatment is not cost-effective, or the cost exceeds £30,000 per Quality-Adjusted Life Year (QALY). This approach is crucial to avoid compromising our capacity to effectively address other diseases. Balancing the economic viability of orphan drug development with the broader healthcare landscape is essential for maintaining a comprehensive and sustainable approach to disease management.

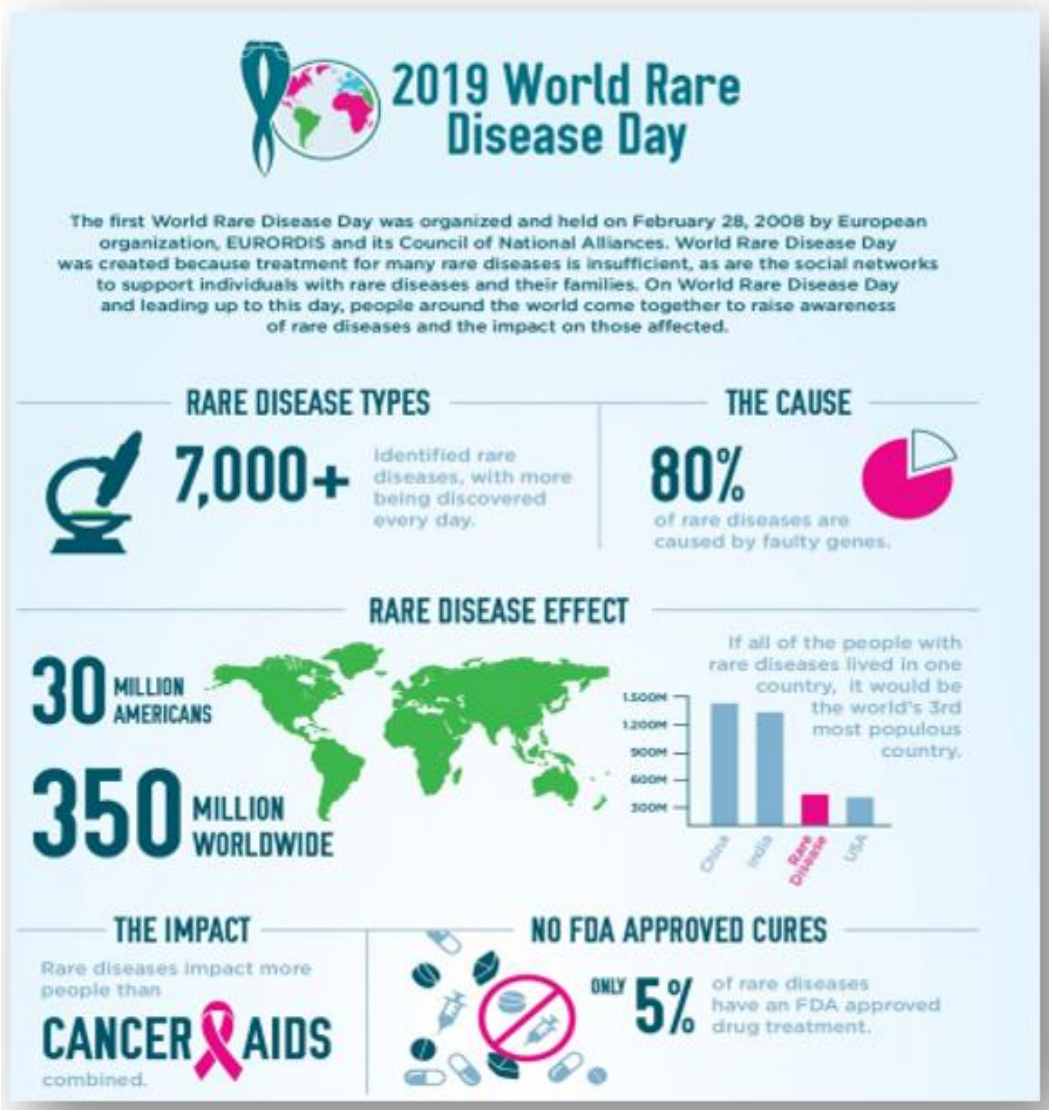

Fig. 1: World Rare Disease Day

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Addressing the Economic Viability of Orphan Drug Development

An orphan drug is a medicinal product specifically designed to treat a rare disease, characterized by its low prevalence and severe impact. Rare diseases, affecting less than 1 patient per 2,000 inhabitants in Europe or no more than 200,000 individuals in the USA, span a vast spectrum of over 7,000 conditions. The global impact is substantial, with over 25 million affected individuals in Europe alone. Despite their individual rarity, rare diseases collectively affect approximately 350 million patients worldwide, surpassing the combined impact of AIDS and cancer. Remarkably, a significant number of these rare diseases lack specific treatments.

Urgency of Addressing Rare Diseases

While rare diseases may affect small numbers of patients individually, their collective impact on a global scale is substantial. The estimate that around 7,000 rare diseases lack specific treatments underscores the urgent need for advancements in the field. Balancing the economic viability of orphan drug development with the broader healthcare landscape is critical to avoid compromising our ability to effectively address a wide range of diseases. Striking this balance is essential for maintaining a comprehensive and sustainable approach to disease management. Many rare diseases have a genetic basis, often affecting newborns, children, and young adults. Due to the rarity of these conditions, physicians may never encounter patients with such diseases in their practice. Consequently, when a baby is born with a rare disease, there is a significant risk that a correct and timely diagnosis may not be made, leading to a delay in appropriate treatment. This underscores the critical need for increased awareness, research, and development of orphan drugs to address the challenges posed by rare diseases and improve outcomes for affected individuals**.** Orphan drugs are the stepchildren of the pharmaceutical industry.

Advancements in Drug Discovery

Industry has historically concentrated on small-molecule drugs, but developments in molecular biology and our understanding of the human genome have expanded our toolkit for drug discovery. Recently, we have added antisense oligonucleotides (ASOs), small-interfering RNAs (siRNAs), gene and cell therapies, and protein-based therapeutics (proteins, peptides, and antibodies). The capacity of these treatment approaches to efficiently target specific cellular compartments or molecular disease pathways varies. While ASOs, siRNAs, gene and cell therapy have expanded the druggable target space to include targets and mechanisms that are challenging to address with small molecules and proteins, such as transcription factor targets and compensation for dysfunctional intracellular proteins, protein-based therapeutics have made it possible to modulate extracellular targets and replace dysfunctional circulating proteins.

Small Molecules

In general, small molecules remain the most well-established therapeutic platform for treating rare diseases. Their methods of administration, regulated dosage, stability, scale of synthesis, and relatively inexpensive cost of products make them appealing as medicinal agents. But the main disadvantage being if a mutated-gene product may not be a druggable target, analysis of the associated pathway may identify a suitable target for small-molecule intervention. Unlike more prevalent diseases, the molecular etiology of rare disorders is frequently well described. Additionally, a number of recent advancements, such as the use of induced pluripotent stem (iPS) cells and gene editing technologies like CRISPR-Cas systems and organoids, have made it possible to develop cellular disease models with a much higher throughput than was

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previously feasible .It is theoretically possible to produce induced pluripotent stem cells (iPS cells) from a skin biopsy sample of a patient and develop them into the desired cell type that expresses the phenotypic characteristic of the disorder. A patient with spinal muscular atrophy (SMA) provided the fibroblasts for one of the earliest high-throughput screenings utilizing iPS cells, which were then differentiated into motor neurons. Some of its major applications include therapeutic small compounds for cystic fibrosis have been identified using cell screens based on an understanding of the underlying mutations in the CFTR gene, which cause abnormalities in protein synthesis, transport. Further candidates are in clinical trials, such as the CNS-penetrant compound ibiglustat for Fabry disease. Two small-molecule LSD (Lysosomal storage disorders) therapies-miglustat and eliglustat for Gaucher disease-and one that functions as a chaperone to stabilize and restore function to a mutant enzyme-migalastat for Fabry disease-are already approved.

Antibody Therapies

Muronomab-CD_3, the first therapeutic monoclonal antibody (mAb), was authorized in 1986 to treat organ allograft rejection. But the initial mouse monoclonals were immunogenic and had a short half-life. Since then, four primary methods-phage display, transgenic animals, B cell immortalization, and single B cell sorting-have been established to find and make these mAbs.However, the first mouse monoclonals had a brief half-life and were immunogenic. Since then, four main techniques have been developed to find and produce these mAbs: phage display, transgenic animals, B cell immortalization, and single B cell sorting. In rare diseases, antibody therapy can be used in several ways some of them include-

Monoclonal Antibodies (mAbs): These are synthetic antibodies made in a lab that are intended to resemble the immune system's defense against aberrant cells or dangerous infections. Monoclonal antibodies can be designed to specifically target proteins or cells involved in the disease process in uncommon disorders. For instance, mAbs have been created to block aberrant proteins in certain genetic disorders or to target particular immune cells in autoimmune diseases.

Antibody-drug Conjugates (ADCs): Antibody-combatant chemotherapeutic drugs, or ADCs, are a class of targeted cancer therapy. By specifically targeting proteins on cancer cells, the antibody minimizes damage to healthy cells while delivering the chemotherapeutic drug directly to the cancer cells. ADCs are being investigated for their potential in treating specific uncommon disorders where focused pharmaceutical administration is required, despite their primary usage in cancer treatment.

Plasma Exchange (Plasmapheresis): This method is taking out the patient's plasma, or the liquid portion of blood, and substituting it with either plasma from a healthy donor or plasma from another patient. Certain rare autoimmune illnesses, such Guillain-Barré syndrome or myasthenia gravis, where the immune system produces antibodies that assault healthy organs, are treated by plasma exchange. A patient's plasma can be exchanged in order to remove dangerous antibodies, which can help lower disease activity and relieve symptoms.

Some of the highly used therapies include Emicizumab, one of the two BsAbs that have been licensed to date, is used to treat a rare condition. It works by binding to factor IX and factor X, bringing these proteins near to one another and starting a coagulation cascade. Recently, caplacizumab, a novel nanobody therapy that targets von Willebrand factor, was approved.

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Protein Replacement Therapies

Protein replacement therapy is a type of treatment used in the management of certain rare genetic disorders characterized by deficiencies or abnormalities in specific proteins. This approach involves administering the missing or defective protein to patients in order to restore its function and alleviate symptoms associated with the disease.

Handling of Missing Proteins: PRT attempts to give patients the precise proteins that they are either lacking or not making in enough amounts. The treatment compensates for the shortage and enhances general health by supplementing these proteins. Protein replacement therapy for rare disease - Stellarix.

Approaches to Developing Protein Replacement Therapy

- ✓ **Gene therapy:** In order for host cells to produce therapeutic proteins, desired genes must be inserted into the cells. It deals with hereditary deficits or illnesses.
- ✓ **Protein engineering:** Modifying proteins improves their effectiveness, specificity, and stability. It helps people with a range of illnesses, including as deficits in certain enzymes.
- ✓ **Transgenic animals:** As affordable bioreactors for protein replacement therapy, genetically modified animals-such as transgenic mice-produce therapeutic proteins.
- ✓ **Nanotechnology:** By creating nanoparticles, therapeutic proteins may be delivered specifically, increasing treatment effectiveness and reducing adverse effects.

Oligonucleotide Therapies

A more comprehensive approach to precisely target genes linked to illness is to do RNA-level interventions. Numerous methods have been devised to target RNA; the most studied being ASOs and siRNAs, which can both lower the production of a particular disease-associated protein by encouraging the breakdown of its mRNA. Similar to antibodies, antisense oligonucleotides (ASOs) and siRNAs have the potential to be extremely focused treatments for uncommon illnesses with a known genetic etiology. A further benefit is that, unlike cell-surface or circulating proteins, any gene product may potentially be targeted.

This therapy can be used by following ways:

Modulate RNA splicing: Targeting certain pre-mRNA sequences with oligonucleotides can change the splicing process and produce functional protein isoforms. This method is applied to disorders including Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) that result from splicing mutations. Inhibit gene expression: Small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) can be utilized to selectively target and destroy disease-causing RNA molecules, which will lower the synthesis of damaging proteins. This method is utilized for disorders like amyloidosis and Huntington's disease that result from the overexpression or aberrant synthesis of certain proteins.

Promote RNA editing: By focusing on certain RNA sequences and using the body's natural RNA-editing resources to alter mutations that cause illness, oligonucleotides can be utilized to induce RNA editing. This strategy is being investigated in disorders including some types of hereditary retinal dystrophies that are brought on by single nucleotide mutations.

Gene and Cell Therapy

There are two broad situations in which gene therapy using viral vectors can be applied for uncommon disorders. For illnesses when the intention of treatment is to make up for a function loss of a certain protein, such in SMA, the vector is utilized to generate a transgene

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that, under the guidance of the proper promoter, encodes the desired protein (optimized codon or endogenous sequence). Conversely, a transgene that encodes an RNA (such a short hairpin RNA) that may use RNA interference processes to decrease gene expression can be introduced for disorders like Huntington disease, where the goal is to suppress the influence of a harmful gene.

Drug and Target Repurposing

Drug repurposing, also known as drug rescue, drug repositioning, drug reprofiling, retasking, or therapeutic switching, entails assessing authorized or experimental medications to address conditions other than those for which the product has been licensed or studied in a clinical setting. The majority of repurposed substances have previously proven safe for humans, and several have advanced to phase II or phase III trials. Theoretically, then, these molecules may be clinically examined for several purposes, offering a speedier, less hazardous, and less expensive route to an authorized medicine than for a whole new treatment.

Two examples where drugs originating from different platforms discussed earlier have gained additional approvals for rare disease indications following initial approval for a common condition are sildenafil and adalimumab. Adalimumab is a mAb that targets the pivotal inflammatory cytokine tumour necrosis factor (TNF), and was first approved in 2002 for rheumatoid arthritis. It has since gained further approvals for several other inflammatory diseases, some of which are rare, including polyarticular juvenile idiopathic arthritis in 2008 and non-infectious intermediate, posterior uveitis and panuveitis in 2014.

The Realm of Orphan Drugs in Rare Disease Treatment

Orphan drugs are pharmaceutical agents developed to treat rare diseases, which are often referred to as orphan diseases. These diseases affect a small number of people, making it financially unattractive for pharmaceutical companies to invest in the development of treatments. Governments and regulatory bodies provide incentives to encourage the development of orphan drugs. Here are some examples of orphan drugs and the rare diseases they are designed to treat:

Table 1: Orphan drugs and the rare diseases

S. No.	Drugs	Diseases
1.	Symdeko (tezacaftor/ivacaftor) Orkambi ivacaftor/lumacaftor)	Cystic Fibrosis
2.	Gleevec (imatinib)	Gastric Cancer (GIST – Gastrointestinal Stromal Tumors)
3.	Myozyme (a glucosidase alfa)	Pompe Disease
4.	Xenazine (tetrabenazine)	Huntington's Disease
5.	Cerezyme (imiglucerase)	Gaucher Disease
6.	Rilutek (riluzole)	Amyotrophic Lateral Sclerosis (ALS)
7.	Exondys 51 (eteplirsen)	Duchenne Muscular Dystrophy
8.	Trisenox (arsenic trioxide	Acute Promyelocytic Leukemia (APL)
9.	Fabrazyme (agalsidase beta)	Fabry Disease
10.	Cinryze (C1 esterase inhibitor)	Hereditary Angioedema

These examples highlight the diversity of rare diseases and the corresponding orphan drugs that have been developed to address them. Keep in mind that the landscape of orphan drugs is continually evolving as new treatments are developed and approved.

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CONCLUSION

The field of orphan and rare diseases is dynamic, with ongoing research, new discoveries, and continuous efforts to improve treatments. Patients with these conditions often face significant medical, social, and economic burdens, and the development of orphan drugs represents a critical step in addressing their unmet medical needs.

Competing Interest Statement

All authors declare that there is no conflict of interests regarding publication of this paper.

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