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Research Article

ORPHAN DRUGS IN TREATING RARE DISEASES

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ABSTRACT

Rare diseases occur globally at every stage of life. The drugs which are used to diagnose or treat rare medical conditions such as cystic fibrosis, multiple sclerosis, narcolepsy etc. are called Orphan drugs. These drugs are called orphan drugs because pharmaceutical companies do not put enough effort because the amount of money invested by the pharmaceutical company to develop the drug would not be recovered by the sale of the drug. The primary purpose of orphan drugs is to fill a critical void in the treatment landscape by targeting rare diseases that have been historically neglected by pharmaceutical development. While each orphan disease affects only a small number of patients, collectively they impact a substantial portion of the population. Orphan drugs are engineered to provide effective treatment options where none may have existed before, offering hope to individuals and families grappling with the challenges of rare diseases. Around 464 drugs only from oncology received this designation till 2020. Around 5644 drugs were designated orphan status at US-FDA till July 2023.

INTRODUCTION

Industries show less interest in the development of treatment for rare diseases.(1) Orphan drug research is dependent on government incentives.(2,3) Cystic fibrosis was thought to be very rare in India, but genetic analysis has now shown that the disease is prevalent but was undiagnosed earlier.(4) In India, the rare disease and disorder population was 72,611,605 as per published data of national population census of 2011(5) India has reportedly higher rare diseases population than the world.
(6) and in fact, India lacks national legislation for orphan medicines and rare diseases.7) With the prevailing COVID-19 pandemic in 2020, the FDA approved 32 orphan-designated drugs and biological products in orphan drug research and development.(8) The International Rare Diseases Research Consortium, has taken notable initiatives to foster orphan drug development.(9) India Alliance Network is reporting, conducting community screening, disease modeling, creation of registries, and training of physicians.(10) Genomics and other Omics tools for Enabling Medical Decision is another project adopted by the Council of Scientific and Industrial Research (CSIR) to provide low-cost diagnostic genetic assays in the country. It can help early identification and screening of rare genetic disorders. (11) Orphan policies have been benefited both patients and the industry. (12,13) The US Food and Drug Administration (USFDA) has awarded an orphan designation to 4905 products in-development. (14). This has also impacted the overall landscape of innovative drug development.(15,16) Orphan diseases are rare diseases, defined in Europe as having an incidence lower than 5 per 10,000 citizens. It is not unusual for a family doctor to encounter less than one such case per

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year. (17) Lack of profit potential and the costs and logistics necessary to organize clinical trials for these pathologies, the development of specific therapies is not a priority for pharmaceutical companies. (18) Beginning in 1982, signs of progress were made concerning the research in this field, with the foundation of the National Organization for Rare Diseases (NORD). (19) Spinal muscular atrophy is a rare autosomal recessive neuromuscular disease, with an incidence of 1 in 10,000 cases. (20)

In the United States, the Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, specifically "any disease or condition that affects fewer than 200,000 people in the United States", or about 1 in 1,500 people. (21)

Rare diseases-Research

Extensive public-private partnerships, including the National Institutes of Health (NIH) and the rare diseases community, which is seeing a renewed industry interest in smaller niche markets, have resulted in an increase of interventions for rare diseases. Significant collaborative efforts are required among the pharmaceutical industry, foundations, patient-advocacy groups, academic and government investigators and funding programs, regulatory scientists, and reimbursement agencies to meet the unmet diagnostic and treatment needs for approximately 25 million people in the United States with 7,000 rare diseases. (22)

Orphan Drugs and Voice of people

Among the 5644 orphan status drugs, top few costliest and rarest drugs were discussed here under:

Riluzole

This drug is primarily to treat amyotrophic lateral sclerosis (ALS), a progressive neurological disease of nerve cells in brain & spinal cord. It prevents release of glutamate from neurons. It also blocks certain voltage gated sodium channels on neurons, thereby reducing abnormal excitability. It increases reuptake of glutamate by astrocytes. It is anti- excitotoxic drug and a review of literature showed minor beneficial effect on both bulbar and limb function, but not on muscle strength. Adverse effects from Riluzole are relatively minor and for the most part reversible after stopping the drug.

Ravulizumab

It is humanized immunoglobulin G2/4K monoclonal antibody that specifically binds to complement protein C5. It blocks terminal complement-mediated inflammation, cell activation and cell lysis. It resulted in immediate and complete terminal complement inhibition (i.e. serum levels of free C5 < 0.5 µg/mL) by the end of the first infusion and throughout the 26-week treatment period in adult. It is used in the rare disease atypical haemolytic uraemic syndrome (aHUS), a type of thrombotic microangiopathy (TMA).

Vutrisiran

It is a subcutaneously administered transthyretin-directed small interfering ribonucleic acid (siRNA) drug directed towards the liver. It is used for the treatment of amyloid transthyretin-mediated (ATTR) amyloidosis, including hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis caused by transthyretin (*TTR*) gene variants . It has received approval in US in June 2022.

Eliglustat

It is a glucosylceramide synthase inhibitor used for Gaucher's disease. Gaucher disease is an autosomal recessive metabolic disorder characterized by accumulation of glucosylceramide (a sphingolipid also known as glucocerebroside) within lysosomes. Eliglustat is broken down to inactive metabolites by CYP2D6 and, to a lesser extent, CYP3A. The patient's metabolizer status of CYP2D6 is determined to titrate the dose of the drug.

Cerliponase alfa

It is FDA approved drug for Batten's disease. It is also known as tripeptidyl peptidase-1 (TPP1) deficiency or late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). It causes slow loss of walking ability in children. The drug is the recombinant form of human TPP and is an enzyme replacement therapy. In randomized clinical trials, Cerliponase alfa showed lesser loss of walking ability compared to untreated patients in the natural history cohort. It is administered as infusion in the cerebrospinal fluid through a intraventricular access device under strict sterile conditions. The adverse effects of the drug include fever, bradycardia, hypersensitivity, increase/ decrease in CSF protein, vomiting, seizures, hematoma, device related infections and hypotension.

Cysteamine

It is a cystine depleting agent used in cystinosis. Cystinosis is a rare disease caused by mutations in the CTNS gene that encodes for cystinosin. A defect in cystinosin function is followed by accumulation throughout the body, especially the eyes and kidneys. This aminothiol drug is used to treat nephropathic cystinosis. The drug reacts with cystine and converts it into a compound that can be readily metabolized or intracellularly transported. The mechanism of action is a cystine disulfide reduction. It has side effects of vomiting and dehydration and any overdose has to be treated symptomatically and in some cases by hemodialysis.

Nusinersen

This drug is for spinal muscular dystrophy which is a autosomal-recessive neuromuscular disorder. There is degeneration of alpha motor neurons leading to progressive muscular weakness and atrophy. It is an antisense oligonucleotide (ASO) which can be the pharmacotherapy for other neurodegenerative disorders as well. The drug effectively modulates splicing of survival motor neuron (SMN) transcripts and animal studies in transgenic mice demonstrated increased SMN protein levels and reduced symptoms of the disease. After an initial saturation period, it has to be applied in the cerebrospinal fluid every four months. The main side effects of nephrotoxicity, blood clotting disorders and thrombocytopenia have to be watched for.

Eculizumab

It is a humanized monoclonal antibody indicated for paroxysmal nocturnal hemoglobinuria (PNH) and reduces complement mediated hemolysis. It is targeted against complement C5, prevents cleavage of C5 into C5a and C5b, thereby preventing deployment of final complement system. Eculizumab is also used to treat neuromyelitisoptica

spectrum disorder in adults who are anti-aquaporin-4 (AQP4) antibody positive. PNH patients should be vaccinated against *Neisseria meningitides* before treatment with eculizumab, since this predictably increases their susceptibility to meningococcal infection. Increased susceptibility to other infections (e.g. urinary, respiratory and gastrointestinal) also occur. It carries a black box warning for risk of meningococcal infections

ZOLGENSMA (Onasemnogene abeparvovec-xioi)

"Zolgensma" world's costliest drug ever $2,125,000 (Indian Rs.18 Crores/dose) of Novartis is a gene therapy for Spinal Muscular Atrophy (SMA) a very rare inherited genetic disorder caused by survival motor neuron-1 gene that is missing or not working properly in the affected person where the patient suffers inability in using his/her arms, legs throat and many other areas in the body. The gene is placed inside a delivery vehicle called vector1 . The vector helps deliver the SMN gene to motor neuron cells throughout the body. The vector that delivers the SMN gene is made from a virus called adeno-associated virus 9, or AAV91 . This is one of the most orphaned drugs because only 2500 patients were treated with this drug till now since its approval in 2019 though affected are being one in 10,000 people worldwide.

Zokinvy (Lonafarnib)

Used in treating Hutchinson Gilford Progeria syndrome a disorder that ages children rapidly. It is the second costliest drug in the world. It is used twice a day with a year's supply worth more than 1 million dollars. It is expected to be used by the affected approximate 400 patients worldwide. It has been placed in the Orphan drug list.

Luxturna (Voretigene neparvovec)

It is used in a kind of inherited eye disorder called Retinal dystrophy. It is a one-time injection given intraocularly costing around $ 850,000. It is manufactured by Novartis Switzerland. It has been placed in the Orphan drug list.

Ravicti (Glycerol Phenylbutyrate)

It is an oral solution in 25ml vials costing $5000/- per vial where annual treatment can cost around $800,000. It is used in treating Urea cycle disorders. The prevalence is one in 440,000 people. It has been placed in the Orphan drug list.

Carbaglu (Carglumic acid)

Carbaglu is 200mg tablet consisting of carglumic acid. It is used to treat patients with elevated ammonia levels in their blood. Each tablet costs $200/- the dosing is high that its annual treatment may amount to $800,000. The occurrence of this disorder is as similar as Urea cycle disorder that is 1 in 440,000 people.

Soliris (Eculizumab)

It is a selective immunosuppressant drug used for the treatment of rare group of red blood cell diseases, paroxysmal nocturnal hemoglobinuria, atypical Hemolytic Uremic Syndrome, Myasthenia Gravis and NeuromyelitisOptica. It is an intravenous injection costing around $6800 per 10mg injection where annual cost may amount to $700,000.

Brineura (Cerliponas ealfa)

Cerliponase alfa is an enzyme replacement treatment for batten disease, a fatal disease of nervous system that typically begins in childhood. Over time affected children experience mental impairment, worsening seizures and progressive loss of sight speech and motor skills. It is a rare disease occurring at the rate of one in 12500 births worldwide. The treatment lasts as long as it remains beneficial to the patient. Annual treatment costs around $700,000. It has been placed in Orphan drug list.

Elaprase (Idursulfase)

Elaprase is an orphan drug which is used in a rare inherited disorder Hunter syndrome that affects only males. Large sugar molecules called glycosaminoglycans (mucopolysaccharides) build up in body tissues. It is a form of lysosomal storage disease. Lack of Iduronate-2-sulphatase enzyme causes heparin sulphate and dermatan sulphate to accumulate in the body tissues. The cost of 6mg vial is $4215 and annual treatment costs around $660,000. Frequency is noticed as one in 150,000 births.

Lumizyme (Alglucosidase alpha)

This drug used in rare inherited disorder called Pompe disease, where complex sugar called glycogen builds up in the body cells. Hence it is named as Glycogen storage disease type-II. 50mg vial costs $870 and annual treatment costs around $520,000. An estimate says around 10,000 people are suffering from this disease worldwide. It has been placed in the Orphan drug list.

Spinraza (Nusinersen)

Nusinersen is used to treat Spinal Muscular Atrophy (SMA). 12mg vial is given to spine by trained personnel, where in the first drug in this list is also meant for SMA. The drug is dispensed in 12mg vials and the annual treatment costs around $750,000 in the first year and $375,000 in the subsequent years. The occurrence is one in 10,000 people.

Rare Disease Policy

Globally as well as in India, rare or orphan diseases as they are also known, pose a significant threat not just to the public health system but also to the country's economic burden. Not to mention the catastrophic impact on families in terms of emotional as well as financial drain, as the cost of treatment is prohibitively high.

How can we solve this problem?

Before India loses any more patients to rare diseases that can be cured with timely treatment, the obstacles blocking the policy implementation need to be urgently addressed. This becomes apparent when one looks at frequent hospitalizations of several rare disease patients for complications arising out of their rare diseases.(23)

Rare diseases

Cystic fibrosis

Cystic fibrosis affects the cells that produce mucus; sweat and digestive juices are affected by Cystic fibrosis. Indians may have a higher prevalence of cystic fibrosis. The tubes, ducts and air passageways are plugged by thick, sticky mucus. Cough, repeated lung infections, fatty stools are the main symptoms of cystic fibrosis. It is a life-limiting, genetic disease of the Caucasians, and Indians. Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes a cAMP-regulated anion channel.

Cystic fibrosis was thought to be very rare in India, but genetic analysis has now shown that the disease is prevalent but was undiagnosed earlier. India has reportedly higher rare diseases population than the world average, but initiatives from government side are still less. (24)

Spinal muscular atrophy (SMA)

It is often wrongly diagnosed as motor neuron disease or as a myopathy. Spinal muscular atrophy (SM) is an inherited disease that affects nerves and muscles, causing muscles to become increasingly weak. It mostly affects infants and children but can also develop in adults. It can damage and kill specialized nerve cells in the brain and spinal cord (motor neurons). Motor neurons control movement in the arms, legs, face, chest, throat, and tongue, as well as skeletal muscle activity, such as speaking, walking, swallowing and breathing.

Pompe's disease

It happens when the body can't make a protein that breaks down a complex sugar, called glycogen, for energy.

Too much sugar builds up and damages muscles and organs.

Spinal muscular atrophy SMA)

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Hutchinson Gilford Progeria syndrome

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Gaucher's disease.

Eliglustat is a glucosylceramide synthase inhibitor used for Gaucher's disease. It is an inherited genetic disorder. It causes bone pain, anemia, enlarged organs, a swollen, painful belly, and bruising and bleeding problems.

Clinical characteristics

GD type 1 is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. GD types 2 and 3 are characterized by the presence of primary neurologic disease; in the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute.(25)

Amyotrophic lateral sclerosis (ALS)

Riluzole drug is primarily to treat amyotrophic lateral sclerosis (ALS), a progressive neurological disease of nerve cells in brain & spinal cord. It prevents release of glutamate from neurons.

Batten's Disease

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Retinal Dystrophy

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Sickle cell anemia

The sickle mutation results in the substitution of valine in place of glutamic acid in the 6 th position of Beta chain. Sickle cell disease is an autosomal recessive blood disorder that can lead to anemia.It is caused by a mutation in the hemoglobin gene, which leads to deformation of red blood cells. Deformed red blood cells can obstruct small vessels and they are prone to destruction. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape. Many of them burst apart as they move through your blood vessels. The sickle cells usually only last 10 to 20 days, instead of the normal 90 to 120 days. The sickle-shaped cells can also stick to vessel walls, causing a blockage that slows or stops the flow of blood. When this happens, oxygen can't reach nearby tissues. The lack of oxygen can cause attacks of sudden, severe pain, called pain crises. These attacks can occur without warning.

Rare Diseases Challenges

Rare diseases occur globally at every stage of life. Patients, families and caregivers have many unmet medical and social needs leading to extraordinary psychosocial and economic burdens. The field of rare diseases is complex and heterogeneous. The landscape of rare diseases is constantly changing, as there are new rare diseases and conditions being identified and reported regularly in medical literature. Challenges facing clinicians who care for affected individuals include gaining knowledge and experience in caring for such patients, and the availability of local experts and of expert guidelines. Finally, there are challenges to investigators regarding the difficulty and expense of assembling large cohorts of affected individuals for study, and garnering funding for research.

Clinical Research in Rare Diseases

The creation of registries and bio banks as research support platforms has made available sources of reliable epidemiological data, allowing the assessment of morbidity and mortality risks and economic and social costs. On the other hand, the availability of high-quality biological specimens allows investigation of the underlying mechanisms of these diseases, developing of new diagnostic techniques and identification of potential therapeutic targets. Thus, initiatives have been launched such as RD Connect, an integrated platform that connects databases, registries, bio banks and clinical bioinformatics for RD research (25)

Another relevant factor is the widespread implantation of electronic health records, which offers access to a large amount of data for each patient, along with the development of software capable of processing this massive volume of biomedical data, including genomic data. Health care big data tools and artificial intelligence allow the development of algorithms for more

accurate detection, diagnosis and treatment of RDs, even in early stages of disease when there is a greater opportunity for intervention. These predictive models, set in the framework of what is known as personalized and precision medicine must be clinically validated before being introduced in clinical practice, a setting where they will facilitate the development of telematic solutions to improve the quality of life of affected individuals and real-time support tools to assist in health care delivery. As for their application in research, the use of artificial intelligence and big data in health care will allow faster recruitment of participants and performance of studies under real-world conditions, yielding evidence on the long-term effectiveness and safety of the interventions under study (26)

National Policy for rare diseases

In the circumstances, though framed with best intent, the policy had implementation challenges and gaps, including the issue of cost effectiveness of supporting such health interventions for limited resource situations, which made it not feasible to implement. Given the challenges in implementing the policy, the need for wider consultation and recommendations, a decision was taken to reframe the National Policy for Treatment of Rare Diseases.

The Future of rare diseases

The future will require a greater understanding and interpretation of available information from multiple sources including electronic health records and big data sources. The pipeline of potential orphan products continues to grow significantly and holds great promise for novel interventions due to advances in clinical trial design and data analyses. Expanding diagnostic procedures with improved sequencing methods will speed up the diagnosis of rare diseases. Accepting agreed upon nomenclature and codification of rare diseases will assist in differentiating diseases and identifying selected sub-populations of rare diseases. Improvements in patient recruitment and increased flexibility in the product review and approval procedures by regulatory agencies will facilitate product approvals. Children particularly will need help and assistance dealing with feelings of isolation from their peers due to their rare disease.(27)

Prevention

Cystic fibrosis disease can be prevented from being passed on to future generations by prenatal genetic screening. Interestingly, CF is also present in adults. Infertility is another symptom. 80%-90% of Cystic Fibrosis mutation in adult males causes 'Obstructive azoospermia' which is due to congenitally absent vas deferens. Lung transplantation is the only option to push life expectancy. Hence, gene-corrected airway stem cells are an alternative strategy. Cystic fibrosis tests may be recommended for older children and adults who weren't screened at birth.In areas where the prevalence of HbS is high,it is suggested that women should be screened in antenatal clinics for sicking trait by sicking test. and hemoglobin electrophoresis. Those diagnosed as HbS trait should have their
husbands examined, and if he is also an HbS trait, then the baby is at risk of getting sickle cell anemia. Chronic villus biopsy sampling at 10- 12 weeks of gestation is advised. Fetal DNA should be analyzed for sickle mutations and if the baby is homozygous, pregnancy should be terminated.

Global approaches of rare diseases

The pipeline of new therapies provides hope to untreated patients. Advances in medical bioinformatics, artificial intelligence and machine learning with access to big data continue to identify novel therapeutics for screening and evaluation. Advanced analytics can identify the patterns of disease occurrence, predict disease progression, identify patient response to treatments, establish optimal care guidelines and generate research hypotheses with the narrowly identified research patient populations.(28)

CONCLUSION

The status of 'Orphan Drug' label depends on legislation of that particular country. 'Orphan Drugs' that are intended to treat rare diseased conditions would be produced profitably by Pharmaceutical manufacturers only with the financial and regulatory support from Governmental agencies. Many of the costs of developing a new drug are incurred regardless of size of potential market. Because the number of people affected with any particular rare disease is very small and the number of rare diseases is so large, a host of challenges complicates the development of safe and effective drugs, and treat for these conditions. A small market is generally viewed as a disincentive for development of pharmaceuticals. The 30 year old 'Orphan Drug Act' has provided many incentives for companies to develop drugs for rare diseases, such as Seven year marketing exclusivity for the first sponsored, exemption of Prescription Drug User Fee Amendments application filing fees, assistance in drug development process, tax credit equal to 50 % of clinical investigation expenses. Regulatory bodies have identified number of problems that sponsors are coming across while doing research on orphan drugs. These include delay in toxicology studies, inadequate chemical compound characterization, poor understanding to characterize pathological processes of disease, poor guidance from Phase I
& II studies to design clinical Phase III studies, inadequate trial designs.

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