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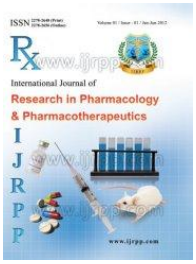

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A review of orphan drugs and rare diseases

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ABSTRACT

The World Health Organization defines orphan diseases, as all pathological conditions, affecting 0.65-1 out of every 1000 inhabitants. They are usually not studied for their path physiology or for newer therapeutic options, as these are not economically viable. The Orphan Drug Act was passed on January 28, 1983 by USA to stimulate the research, development, and approval of those products that treat orphan diseases. Till date, 11 drugs (4.87%) for tropical infectious diseases has been designated with orphan drug status, and as many drugs for other infectious diseases. Several drugs with orphan status are used in the treatment of diseases that no longer meet orphan status criteria, such as AIDS and end-stage renal disease. Understanding of the human genome, nuclear cloning, rational drug designing, and application of high throughput screening in drug discovery programs, might lead to new drug discoveries for orphan diseases. Hence, there is hope in the future for patients neglected by for-profit drug discovery efforts.

Keywords: Newer Therapeutic Options, Orphan Drug Act, Drug Discovery Programs.

INTRODUCTION

A conventional sampling approach in an epidemiological study is not suitable for rare diseases because of their extremely low incidence rates. Epidemiological data, such as disease prevalence is particularly useful in establishing health care policies for patients with rare diseases. In developed countries such as the United States, patient registries are used to obtain key epidemiological data on rare diseases, but data on only some of those diseases are available[1]. Rare diseases, when taken together, are not that rare at all. In fact, according to the National Institutes of Health (NIH), 30 million Americans have one of the nearly 7,000 diseases that are officially deemed "rare" because alone they each affect fewer than 200,000 people in the United States. Sometimes, only a few hundred patients are known to have a particular rare disease[2].

Rare diseases in small patient populations, thus "orphaned" by the pharmaceutical trade, having an insufficient approved drug treatment options available are called "orphan diseases." A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical disorder, the condition itself being stated as "orphan disease". Drugs for rare disease, which are not invented by the pharmaceutical industry for economic reasons but which is developed with the

intention to public health prerequisite[3]. The indications of a drug may also be considered as "orphan" since a substance may be used in the treatment of a frequent disease but may not have been intended for another more rare disease.

Many orphan diseases are lesser known, like Juberg Marsidi syndrome (a genetic disorder of childhood that leads to severe mental retardation, abnormal bone growth resulting in the disfiguring of the head and body and loss of hearing), Hermansky-Pudlak syndrome (a group of genetically heterogeneous disorders which share the clinical findings of oculocutaneous albinism, platelet storage pool deficiency and ceroid lipofuscinosis), Werdnig Hoffman disease (a fatal, fetal disease similar to amyotrophic lateral sclerosis (ALS), Omenn's syndrome (absence of mature B and T cells, children being born with late-stage ALS-like symptoms), Fabry's disease (an X-linked lysosomal-storage disorder due to deficiency of galactosidase A), Lambert-Eaton myasthenic syndrome (an autoimmune disease of peripheral cholinergic system resulting in muscle weakness due to impaired acetylcholine release), and many more like Aarskog syndrome, Adams Nance syndrome, Bagatelle Cassidy syndrome, Bamforth syndrome Ballard syndrome and Bahemuka Brown syndrome[7,9,11].

THE CONCEPT OF RARITY

"A rare disease is a disease that occurs infrequently or rarely in the general population". In order to be considered as rare, each specific disease cannot affect more than a limited number of people out of the whole population. It is important to underline that the number of rare disease patients varies considerably from disease to disease, and that most people represented by the statistics in this field suffer from even rarer diseases, affecting only one in 100,000 people or less[8, 20].

Rare Diseases

Rare diseases are characterized by their low prevalence (less than 1/2000) and their heterogeneity. Because rare disease patients are a minority, there is a lack of public awareness; these diseases do not represent a public health priority. The market is so narrow for each disease that the pharmaceutical industry is reticent to invest in research to develop and to develop treatments for rare diseases. There is therefore a need for economic regulation, such as national incentives[13, 16].

Orphan diseases

Orphan diseases comprise both rare diseases and neglected diseases. They are "orphan" of research focus and market interest, as well as public health policies. The World Health Organization defines orphan diseases, "as all pathological conditions, affecting 0.65-1 out of every 1000 inhabitants". They are usually not studied for their pathophysiology or for newer therapeutic options, as these are not economically viable[13, 15, 24].

Orphan Drugs

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of rare diseases. These drugs are called "orphan" because, under normal market conditions, it is not cost-effective for the pharmaceutical industry to develop and market products are intended for only a small number of patients suffering from rare conditions[34, 36]. For drug companies, the cost of bringing an orphan medicinal product to the market would not be recovered by the expected sales of the product. For this reason, governments and rare disease organizations have emphasized the need for economic incentives to encourage drug companies to develop and market medicines intended for the "orphaned" rare disease patients.

Need for orphan drug regulation

Absence of specific treatment for orphan disease causes psychological distress to the patient and the family, and a feeling of hopelessness sets in. Many diseases lacking specific therapy are important targets for anecdotal therapy. Thus, unproven therapies and wrong beliefs prevail in quest of some relief. USA was the first nation to propose a legal framework to encourage the development and availability of orphan drugs. The Orphan Drug Act (ODA) was passed on January 28, 1983, which was an amendment of Federal Food, Drug, and Cosmetic Act of 1938, to stimulate the research, development, and approval of products that treat orphan diseases[26, 28]. Drugs are granted orphan status for a specific indication, and still need studies to demonstrate their safety and efficacy, unless these qualify for accelerated approval.

The main incentives for achieving orphan drug status (ODS) include:

- Tax incentives for clinical research,
- Study design assistance from the FDA,
- Exemption from application-filing fees,
- Grant for Phase I and II clinical trials, and
- Seven years of marketing exclusivity after the approval of the drug or biological product.

More than 10 million patients have been treated since the inception of ODA, which has fuelled research of orphan diseases. ODA exists in various countries like USA, Japan, Singapore, Australia, Canada, France, Sweden, and the United Kingdom. The basis of the initiative of other countries being the US ODA, with variations like marketing exclusivity rights to the marketing company for 7 years in USA, 10 years in Japan, and 5 years in Australia. Other countries seeking to establish similar legislation include South Korea, New Zealand, and India. A group of pharmacologists requested the Indian government to institute ODA at the conference held by the Indian Drug Manufacturing Association in November 2001, but nothing concrete has materialized so far.

Statistics of Rare Diseases

About 6000-8000 rare diseases have been affecting 7% of the population worldwide. 95% of medical conditions included in rare list have no FDA approval treatments. 80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes According to San Orphan SA, Geneva, Switzerland, around 65 per cent of rare diseases is serious and disabling. Most interestingly, about 250 new rare diseases are discovered each year, corresponding to five new rare diseases per week[22, 25].

Genetic skeletal diseases

Genetic skeletal diseases (GSDs) are an extremely diverse and complex group of rare genetic conditions that primarily affect the development and homeostasis of the osseous skeleton. Although individually rare, as a group of related genetic diseases, GSDs have an overall prevalence of at least 1 per 4,000 children, which extrapolates to a minimum of 225,000 people in the European Union. This burden in pain and disability leads to poor quality of life and high health care costs. There are more than 450 unique and well-characterized phenotypes that range in severity from relatively mild to severe and lethal forms and are described in detail in the 2011 Nosology and Classifications of the GSDs. Forty different diagnostic groups have been recognized to date, which are defined by a combination of molecular, biochemical and/or radiographic criteria. The 2011 Nosology includes 316 conditions associated with one or more of 226 different genes; however, the continued genetic and molecular characterization of GDSs has led to a better defined clinical-molecular classification and a greater understanding of their aetiology[14, 19].

ORPHAN DRUGS IN THE PIPELINE FOR RARE DISEASES

Potential New Treatment for a Genetic Disease in Infants

Hypophosphatasia is a rare inherited bone disease that results from a genetic mutation which hinders the formation of bones and teeth and can result in substantial skeletal abnormalities. Severely affected infants often have persistent bone disease or die from respiratory insufficiency due to progressive chest deformity from poorly developed bones. Currently, there are no approved medicines for this disease. One therapy in development delivers the enzyme necessary for proper bone growth that patients with hypophosphatasia are missing[21, 29].

Combination Vaccine Treatment for Pancreatic Cancer

A potential treatment for pancreatic cancer is a combination of two therapeutic vaccines. The treatment combines a Listeria based vaccine that has been engineered to express the tumour-associated antigen mesothelin and allogeneic pancreatic cancer cells that are genetically-modified to secrete the immune-stimulant, granulocyte-macrophage colony stimulating factor (GM-CSF). The cells are irradiated to prevent further cell growth, although they stay metabolically active. Sequential administration of the vaccines in animal studies has demonstrated enhanced tumour-specific T-cell and antitumor responses.

Two Targets to Fight Leukemia

A potential first-in-class medicine for acute lymphoblastic leukemia (ALL) is a bispecific T-cell engager antibody designed to focus the body's cell destroying T-cells against cells expressing CD19, a

protein found on the surface of B-cell-derived leukemia and lymphoma. The modified antibodies are designed to engage two different targets simultaneously, linking the T-cells to cancer cells[31, 40].

Pompe disease

Pompe disease also referred to as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid-glucosidase (GAA). It was the first recognized lysosomal storage disease and is the only glycogen storage disease that is also a lysosomal storage disease. In Pompe disease, lysosomal glycogen accumulates in many tissues, with skeletal, cardiac, and smooth muscle most prominently involved. Alglucosidase alpha - The U.S. Food and Drug Administration approved Lumizyme an enzyme replacement therapy (ERT) orphan drug for patients ages 8 years and older with late onset (non-infantile) Pompe disease.

Treatments for Patients with Debilitating Lung Disease

Idiopathic pulmonary fibrosis (IPF) is a debilitating and almost uniformly fatal disease in which patients experience, progressive difficulty breathing due to scarring of the lungs. There are currently no effective treatment options available, and the average patient with IPF dies within three years of diagnosis. A medicine in development targets connective tissue growth factor, which is elevated in the lungs of IPF patients. Researchers recently announced promising results from a Phase II trial in which 60 percent of IPF patients were able to stabilize their disease or experience improvement in lung function[28, 31].

Raynaud's phenomenon

Raynaud's phenomenon (RP) is a condition resulting in a particular series of discolorations of the fingers and/or the toes after exposure to changes in temperature (cold or hot) or emotional events. Skin discoloration occurs because an abnormal spasm of the blood vessels causes a diminished blood supply to the local tissues initially, the digit involved turn white because of the diminished blood supply. The digit, then turns blue because of prolonged lack of oxygen. Finally, the blood vessels reopen, causing a local "flushing" phenomenon, which turns the digit red. This three-phase colour sequence (white to blue to red), most often upon exposure to cold temperature, is characteristic of RP. Iloprost is a synthetic analogue of prostacyclin PGI2. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation. The two diastereo isomers of iloprost differ in their potency in dilating blood vessels, with the 4S isomer substantially more potent than the 4Risomer.

Orphan Drug Approvals for Rare Diseases

Zelboraf (vemurafenib), a personalized medicine, was approved for the treatment of unresectable or metastatic melanoma that expresses a gene mutation called BRAF V600E. It was approved with a first-of-its-kind companion diagnostic (4800 BRAF V600 Mutation Test) to help determine if a patient has the gene mutation. A normal BRAF protein is involved in regulating cell growth but a mutated form is found in about half of the late-stage melanoma cases. Zelboraf is able to block the function of the V600Emutated BRAF protein.

Adcetris (brentuximab vedotin), the first in a new class of antibody-drug conjugates (ADCs), was approved to treat Hodgkin lymphoma and systemic anaplastic large cell lymphoma (ALCL), a rare type of lymphoma that represents only 3 percent of all non-Hodgkin lymphomas. ADCs combine a monoclonal antibody and a therapeutic drug, where the antibody directs the therapeutic to target the cancerous cells. It is also the first FDA-approved drug for Hodgkin lymphoma in more than 30 years and the first to specifically treat ALCL. The actress is composed of an anti-CD30 monoclonal antibody and a microtubule disrupting agent, allowing it to release its therapeutic drug once inside the CD30-expressing tumor cells[42].

Kalydeco™ (ivacaftor) was the first medicine approved to treat the underlying cause of cystic fibrosis (CF) and not just the symptoms of the disease. It targets a defective protein to help achieve sustained improvement in lung function. Kalydeco was approved for use in people with cystic fibrosis (ages 6 and older) who have at least one copy of the G551D mutation in the CF transmembrane conductance regulator (CFTR) gene. The defect affects a small portion of CF patients about 5 percent or 1,200 of the 30,000 CF sufferers, but it also provides hope that the knowledge gained will lead to treatments that will help even more CF patients[44, 47].

CONCLUSION

The success of orphan drug designation for neglected rare diseases shows that companies using orphan drug programs can generate profits and recoup their R&D investments even with relatively small markets in the developed world. The orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills. The orphan drug designation should be promoted in various countries, not having their regulations for such categories of diseases, to promote the treatment for sufferers with rare diseases.

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