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Review Article

Evaluation of orphan drug therapies and associated monitoring guidelines

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ABSTRACT

Orphan drugs, designed for the treatment and prevention of rare medical conditions known as orphan diseases, are infrequently accessible due to their high costs and limited research. The prevalence of rare diseases varies across countries based on population demographics. The Food and Drug Administration (FDA) has approved over 770 drugs with 77 designations for orphan status. Some of these drugs, often discovered by the pharmaceutical industry, are both highly valuable and expensive. When using orphan drugs, specific parameters need to be monitored. Therapeutic monitoring should align with the patient's physical condition and the severity of the disease. This article aims to comprehensively examine the development of orphan drugs and their monitoring protocols.

Keywords: Orphan diseases, Orphan drugs-development, Therapeutic monitoring, Disease severity, Monitoring criteria

INTRODUCTION

Orphan diseases, characterized by their rarity and occurrence predominantly in regions with high population density, exhibit a higher prevalence in developing countries compared to developed ones. These diseases acquire the term "orphan" due to the challenges associated with developing treatments for conditions that affect a small percentage of the population. Notable examples of rare diseases encompass Kahler's disease (Myelomatosis), Hodgkin's lymphoma, Lou Gehrig's disease, Spina bifida, Apert syndrome, among others. According to the criteria established in the United States, an orphan disease is one that affects fewer than 200,000 people.[1]

The global impact of orphan diseases is significant, given that each country only addresses a fraction of the affected population. Diagnosing rare diseases often proves challenging and time-consuming, with delays of several years attributed to difficulties in diagnostic modalities and insufficient awareness among healthcare professionals. In numerous instances, there are no existing diagnostic methods for many rare diseases, exacerbating the global burden they impose.

To address this kind of challenging scenario, the development of orphan drugs has emerged as a pivotal strategy. These specialized pharmaceuticals aim to provide effective treatments for rare diseases, offering hope and targeted solutions in the face of limited therapeutic options.[2]

DEVELOPMENT OF ORPHAN DRUGS

Orphan drugs, formulated to address diseases or disorders occurring infrequently, confront a distinctive set of challenges hindering their widespread production. These conditions are often so uncommon that pharmaceutical

companies deem it financially impractical to produce them without governmental assistance. As a result, obtaining licenses for the manufacturing of orphan drugs becomes a daunting endeavor, with the exorbitant costs serving as a substantial deterrent for pharmaceutical firms. These medications, typically derived from biological products employed in diagnosing, treating, and preventing rare diseases, hold particular significance in regions with limited resources, where endemic rare diseases prevail.[3]

The market availability of orphan drugs remains restricted, and despite ongoing research efforts by some pharmaceutical companies, the developmental journey from discovering a new drug molecule to its market presence is protracted, uncertain, and demands substantial capital investment. Although addressing public health needs, the disadvantages inherent in orphan drug development are notable. The primary impediment lies in the astronomical costs associated with the research, development, and marketing of orphan drugs. The expectation of recovering these costs from the sales of such drugs is unrealistic, given the lack of interest in their manufacturing. While these drugs may be life-saving for a select few, their commercialization proves challenging. To overcome this hurdle, governments can offer tax benefits and incentives to pharmaceutical companies, a strategy exemplified by the United States through the enactment of the Orphan Drug Act in 1983 under the administration of President Ronald Reagan.[4]

The FDA additionally guarantees that drugs submitted by private companies meet all essential requirements, mirroring the standards set for common disease therapies. This includes the scrutiny of small molecules in pills and tablets, as well as large molecules such as biologics derived from living substances, governed by the Public Health Services Act-Section 351. As time has progressed, there has been a rise in the occurrence of orphan diseases impacting larger populations, resulting in an increased in industrial research dedicated to orphan drugs.

The Orphan Drug Act has played a crucial role in addressing pricing concerns related to orphan drugs. Amendments in 1984 led to the approval of several orphan drugs by the FDA, with approximately 770 drugs discovered and approved in the United States alone. However, challenges persist in developing countries like India, where there is currently no standardized definition of rare diseases and limited data on their prevalence.[5]

EXAMPLES OF ORPHAN DISEASES AND ORPHAN DRUGS

A variety of rare diseases qualify for orphan drug designation, underscoring the importance of specialized medications in addressing these uncommon conditions. Among the notable examples are Hodgkin's lymphoma, cystic fibrosis, porphyria, myelomatosis, polycythemia vera, encephalomyelitis disseminata, methanol intoxication, spina bifida, acquired hemophilia, graft-versus-host disease (GVHD), chronic myelogenous leukemia, and differentiated thyroid carcinoma (DTC).[6]

These orphan drugs, crucial in managing these rare diseases, are enumerated alongside their generic names and trade forms, presenting a comprehensive list of valuable and cost-effective therapeutic options. As per research conducted by Helfand et al in 2013, some of these drugs include acetyl cysteine (Lumenac), 4-amino salicylic acid (Paser), digoxin antibody (Lanoxin), fomepizole (Antizol), factor VIII (Hemorel), human anti-thrombin (AT) IIIs (Thrombate III), thalidomide (Thalomid), erythropoietin drug (Intas), cyclosporine (Esporine), methotrexate (Remtrex), rituximab (Rituxan), lenalidomide (Revlimid), eculizumab (Soliris), everolimus (Afinitor), nilotinib (Tasigna), bortezomib (Velcade), interferon beta – 1a (Avonex), ipilimumab (Yervoy), interferon beta – 1a (Rebif), ruxolitinib (Jakavi), carfilzomib (Kyprolis), factor VII A recombinant (Novo Seven), glatiramer acetate (Copaxone), pemetrexed (Alimta), dasatinib (Sprycel), ivacaftor (Kalydeco), sunitinib malate (Sutent), anti-hemophilic factor VIII recombinant (Kogenate), sorafenib tosylate (Nexavar), and ibrutinib (Imbruvica), among others.

This extensive range of orphan drugs signifies the ongoing efforts to provide effective therapeutic solutions for rare diseases, showcasing the diverse pharmacological advancements contributing to the field of orphan drug development.[7]

ORPHAN DISEASES AND ITS DRUG TREATMENT WITH MONITORING CRITERIA

Hodgkin's lymphoma

These are classified as a rare form of cancer, specifically impacts the body's immune system by causing damage to white blood cells, particularly B-cells, leading to their malignant transformation. In more straightforward terms, Hodgkin's lymphoma is characterized as cancer of the lymphatic system, where white blood cells, specifically affected B-cells, undergo malignancy, resulting in their accumulation in the lymph nodes.[8]

This disease progresses through three distinct stages: stage 1- in this initial stage, only one lymph node is affected by the cancerous cells, stage 2- progressing further, two or more lymph nodes become affected by the cancerous cells, and stage 3- advancing to the third stage, the cancer can extend its impact to both sides of the diaphragm.

The treatment regimen for Hodgkin's lymphoma typically involves a combination of chemotherapy and steroid treatment, such as the administration of Prednisolone. This therapeutic approach aims to combat the malignant cells, halt their proliferation, and manage the disease's progression effectively. Hodgkin's lymphoma, though rare, demands a comprehensive and targeted treatment

strategy to address its unique characteristics within the immune system and lymphatic system.[9]

Myelomatosis

Multiple myeloma, also referred to as Kahler's disease, is an uncommon type of cancer marked by the abnormal and uncontrolled multiplication of monoclonal plasma cells, a distinct subtype of white blood cells, within the bone marrow. This unrestrained proliferation can lead to the generation of non-functional intact immunoglobulin and immunoglobulin chains. The consequences of multiple myeloma encompass the destruction of bones, compromise of the immune system, impairment of kidney function, and disruption of red blood cells.[10]

The disease poses severe threats to various physiological systems, with common causes of death attributable to myelomatosis encompassing bleeding, arising from low platelet counts, complications arising from bone disorders, kidney failure, and the occurrence of blood clots in the lungs. The multifaceted nature of its effects underscores the critical need for a comprehensive understanding and targeted approach in managing this rare and complex form of cancer.

In the treatment of multiple myeloma, Lenalidomide emerges as a primary therapeutic intervention, distinguished by its unique mechanism of action. Lenalidomide functions by augmenting T-cell co-stimulation, thereby fostering cytotoxicity against tumor cells. This targeted mechanism aims to impede the abnormal proliferation of monoclonal plasma cells, providing a focused strategy to mitigate the detrimental effects of Multiple Myeloma on the bone marrow, immune system, and vital organs.[11]

Porphyria

This collection of syndromes pertains to disorders in which porphyrins, crucial enzymes responsible for heme synthesis, function improperly. Dysfunction in these enzymes can impede the conversion of porphyrin into heme, resulting in severe symptoms such as high blood pressure, insomnia, motor weakness, and anxiety. Additionally, individuals may experience minor symptoms, including intense abdominal, back, and limb pain. The three primary types of porphyria are acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria, with the latter being a rare genetic disorder.[11]

The occurrence of hereditary coproporphyria is associated with the presence of a defective gene from one parent, following an autosomal dominant pattern, or defective genes from both parents, following an autosomal recessive pattern.

In terms of treatment, Haemarginate is employed. The mechanism of action involves replenishing the heme stores within the body. This therapeutic approach is essential for managing the symptoms and addressing the underlying deficiency in heme synthesis associated with porphyria.[12]

Chronic myelogenous leukemia

This is an uncommon clonal disease categorized as a myeloproliferative neoplasm, marked by the abnormal growth of hematopoietic cells in the bone marrow. The disease progresses through three distinct phases: chronic, accelerated, and blast, with the presence of immature white blood cells, known as blasts, in both the blood and bone marrow. A notable and severe symptom of chronic myeloid leukemia (CML) is bone pain.[13]

For treatment, Dasatinib is employed. Its mechanism of action involves blocking abnormal proteins that signal cancerous cells to multiply. This targeted approach aims to impede the aberrant cell growth associated with CML, contributing to the management of the disease and alleviation of symptoms, particularly bone pain.[14]

Polycythemia vera

Polycythemia vera is a chronic condition categorized as a myeloproliferative neoplasm. Also referred to as erythrocytosis, it involves an abnormal increase in red blood cell mass. This disorder is characterized by clonal, genetically inherited stem cell proliferation affecting white blood cells and platelets. The primary concern with polycythemia vera is the heightened risk of thrombotic events, or thrombosis, due to the blood's increased viscosity. While it is a rare subtype of polycythemia, there is a potential link to the progression of leukemia in some cases.[15]

Standard therapy for polycythemia vera typically includes the administration of Ruxolitinib. This medication functions by dampening the activity of the immune system and mitigating the overproduction of red blood cells. This targeted approach effectively tackles the root causes associated with the condition.[16]

Differentiated thyroid carcinoma

It is a slowly progressing thyroid carcinoma, representing a rare disorder that manifests as a mass on the thyroid gland. As per the WHO classification, it is primarily categorized into papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC), with FTC being an infrequent subtype of differentiated thyroid carcinoma (DTC). The primary symptom is the development of a benign thyroid nodule.

The recommended treatment involves Sorafenib tosylate. However, before prescribing this medication, surgical therapy and radioactive iodine therapy should be administered. The mechanism of action of Sorafenib tosylate includes the inhibition of tumor growth and angiogenesis in DTC.[17]

Table 1: Orphan drugs overview: diseases, affected areas, categories, mechanisms, and monitoring.

Disease	Affected area/ location	Name of the orphan drug with category	Mechanism of action	Monitoring criteria
Hodgkin's lymphoma	White blood cells (over production of B-cells)- immune system	Prednisolone- corticosteroids	Suppress the migration of polymorphonuclear leucocytes ↓ decreases inflammation ↓ suppress the immune function	Monitor the toxic level – inflammation and blood sugar level thoroughly.[23]
Myelomat-osis, myelomtics pina bifida	Bone marrow (uncontrolled proliferatin of monoclonal plasma cells)	Lenalidomide- immunomodula -tory agent	Increases T-cell co stimulation ↓ Produces cytotoxicity against tumor cells ↓ Inhibiting the proliferation of malignant cells.	Monitor the complete blood counts. For first 12 weeks; the test should be done twice a week. Then once in four weeks until the results are normal.[24]
Porphyria	Porphyrin (enzyme responsible for the synthesis of heme)- RBC	Haemarginate- ferric compound	Reduce the overproduction of gamma aminolevulinic acid that produce the acute symptoms of porphyria ↓ Replenishing the heme stores within the body.	Monitor the level of blood through screening tests (blood tests which show whether the blood is properly clotting or not) and clotting factor tests.[25]
Graft versus host disease (GVHD)	Stem cells, bone marrow	Thalidomide- immunomodula tory agent	Inhibiting the production of myelomatic cells ↓ By blocking the expression of interleukin 6 (IL 6) ↓ Degradation of protein	Monitor the platelet count of the patients and also BP, blood sugar level and allergic reactions such as skin rashes. Also perform liver function test and kidney function tests.[26]
Chronic myelogeno-us leukemia (CML)	WBC, bone marrow	Dasatinibanti- cancer drug	Blockage of abnormal proteins that signals the cancerous cells to multiply	Perform the tests of blood - complete blood count (CBC) Monitor the interactions when consumed with other medications.[27]
Cystic fibrosis	Upper and lower respiratory tract	Ivacaftor, ibrutinib- cystic fibrosis transmembrane conductance regulator (CFTR)	Improve the function of G551D-CFTR gene ↓ Transport of Na+ and Cl- ions across cell membrane ↓ Improve hydration clearing of thick mucus.	Monitor the sodium and chloride ion concentration which produce serious systemic effect and Also monitor the serious adverse event in patients age 18 or older.[28]
Differenti-ated thyroid carcinoma (DTC)	Thyroid gland	Sorafenibtosyla te-kinase inhibitor	Blocks the enzyme RAF kinase ↓ Control of cell division or proliferation ↓ Inhibit the tumor growth and angiogenesis of DTC.	Monitor the liver function tests regularly Also monitor the symptoms such as burning sensation in tongue or mouth ulcers- if it is, consult your physician.[29]
Polycythe-mia vera	Red blood cells (RBC)	Ruxolitinib- anti- cancer drug (kinase inhibitor)	Functions mainly to suppress the immune system, decrease the production of RBC	Monitor the patient's RBC level and urea level (should not exceed 23 mg/dl). Monitor the size of the spleen through physical examination. Monitor the ECG levels of the patients and also

Continued.

Disease	Affected area/ location	Name of the orphan drug with category	Mechanism of action	Monitoring criteria
				monitor the severe reactions such as gum bleeding.[30]
Encephalo myelitis disseminate s	Neurons/axons	Glatiramer acetate – immunomodula -tor	Stimulation of myelin (basic protein) ↓ Insulation of nervefibres in spinal cord ↓ Blocking of myelin damaging T-cells.	Monitor the platelet count of the patients and also monitor the BP, blood sugar level. Also perform liver function test and kidney function tests.[31]
Acquired hemophilia	RBC	Factor VII A recombinant-clotting factor	It mainly works by the inhibition of hemorel factor namely factor VIIA recombinant by autoantibodies leads to clotting of blood.	Monitor the activity of anti-thrombin VII A and the hemoglobin value (> or equal to 12 g/dl) and blood pressure value (normal-120/70 mm Hg).[32]

Cystic fibrosis

Cystic fibrosis is a rare disease characterized by multi-organ defects, primarily impacting the upper and lower respiratory tract, leading to inflammation. It also manifests in the pancreas and reproductive tract. The condition is predominantly a result of genetic abnormalities, specifically an autosomal recessive trait, primarily attributed to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Its prevalence is higher among Caucasian populations, primarily due to the presence of two mutations in the CFTR gene.[18]

The initial indication of cystic fibrosis is a distinctive salty taste to the skin. Subsequent symptoms associated with the disease may intensify over time. The treatment approach involves the use of Ivacaftor and Ibrutinib. These medications operate by enhancing the function of the G551D protein within the CFTR gene, contributing to the improvement of the condition.[19]

Encephalomyelitis disseminates

Encephalomyelitis disseminata, commonly known as multiple sclerosis (MS), is a chronic autoimmune disorder characterized by inflammation and damage to the central nervous system, particularly the brain and spinal cord. The condition arises when the immune system mistakenly attacks the protective myelin sheath surrounding nerve fibers, leading to disruptions in communication between the brain and the rest of the body. This demyelination process results in a diverse range of symptoms, including fatigue, impaired coordination, numbness, and cognitive dysfunction. MS often exhibits a relapsing-remitting pattern, where symptoms flare up and then subside, though it can progress to a steady decline over time. The exact cause of multiple sclerosis remains unclear, but a combination of genetic and environmental factors is believed to contribute to its development. Management of the disease typically involves immunomodulatory medications to alleviate symptoms and slow down the progression of the condition.[20]

Waldenstrom macroglobulinemia

Waldenstrom macroglobulinemia is a rare form of cancer classified as a chronic lymphoproliferative disorder, primarily affecting white blood cells. This malignancy is characterized by abnormal increases in immunoglobulin production, falling under the category of malignant gammopathies. The cancer primarily impacts two types of B-cells: lymphoplasmacytoid cells and plasma cells. In Waldenstrom macroglobulinemia, the bone marrow undergoes excessive production of white blood cells, leading to their accumulation around normal, healthy blood cells. The recommended treatment for this condition is Ibrutinib, which operates by inhibiting the action of the protein kinase enzyme, thereby addressing the underlying mechanisms of the disease.

Acquired hemophilia

Acquired hemophilia is a rare but serious autoimmune disorder characterized by the spontaneous development of inhibitors that attack and neutralize clotting factor VIII, a crucial protein involved in blood coagulation. Unlike congenital hemophilia, which is typically present from birth, acquired hemophilia often emerges later in life. The condition can lead to uncontrolled bleeding, both internally and externally, resulting in symptoms such as bruising, prolonged bleeding from minor injuries, and, in severe cases, life-threatening hemorrhages.[21] Acquired hemophilia is associated with underlying medical conditions, autoimmune disorders, or certain medications. Diagnosis involves assessing clotting factor levels and detecting the presence of inhibitors. Treatment aims to control bleeding episodes and eliminate inhibitors, often involving immunosuppressive medications and replacement therapy with clotting factors. Management is multidisciplinary, involving hematologists,

immunologists, and other specialists to address the complex nature of this acquired bleeding disorder.[22]

MONITORING CRITERIA FOR ORPHAN DRUGS

The following parameters can be considered during orphan drugs administered: patient's individual body conditions, indication of that particular drug, mechanism of that particular drug, and adverse reaction produced by that drug.

CONCLUSION

In conclusion, the development of orphan drugs has become a crucial strategy in addressing the unique challenges posed by rare diseases. These conditions, often overlooked due to their low prevalence, require specialized therapeutic solutions to provide hope and targeted care for affected individuals. The Orphan Drug Act in the United States has played a pivotal role in incentivizing pharmaceutical companies to invest in the research and development of orphan drugs, leading to the approval of over 770 drugs with orphan status.

However, challenges persist, especially in developing countries like India, where the definition of rare diseases is not standardized, and data on prevalence is limited. The high costs associated with orphan drug development remain a significant hurdle, and governments worldwide need to implement strategies such as tax benefits and incentives to encourage pharmaceutical companies to engage in this vital research.[33] As advancements in orphan drug development continue, it is imperative for healthcare professionals and regulatory bodies to collaborate in refining monitoring protocols. This ensures that patients with rare diseases receive optimal care, mitigating the challenges associated with their conditions and offering a brighter future for those affected by orphan diseases.

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