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Status of Orphan Diseases in India

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Abstract: The landscape of rare diseases is frequently changing, as new rare diseases and conditions are being recognized and reported often in medical literature. In India due to lack of a transparent definition and regulatory approval process for rare diseases therefore until now, has constraining pharmaceutical industries from pursuing drug development for rare diseases. Although extremely challenging, considering the intricacy of various diseases and the difficulty in diagnosis, there is a strong need to carry out systematic epidemiological studies to determine the number of people suffering from rare diseases in India.

Introduction

When compared to typical diseases, a rare disease (RD) or an orphan disease is a medical condition with a low prevalence [1,2]. RDs impact about 6% of the total population [3], which is more than 470 million individuals, Around the world, fewer than 10% of RD patients receive treatment tailored to their specific condition [4]. The World Health Organization classifies a rare disease as one that affects ≤1/1000 people. According to the USFDA, a problem affects 200,000 or fewer people at any given time, whereas other criteria include disorders that impact less than 1% of the EU population. Diseases involving less than two patients per 100,000 people are considered very rare. Still, rare illnesses aren't that rare [5]. Between 5000 and 8000 rare diseases are known to exist, and about 7000 of them do not yet have a viable cure. Rare diseases can occasionally progress and are frequently severe and chronic. Although uncommon infections, autoimmune diseases, and malignancies are common, genetics accounts for around half of them. Most of the time, the reasons are still unclear [6]. Experts in medicine are still unable to agree upon a common description of what "rare diseases" are. According to the working definition provided by the World Health Organization (WHO), these illnesses are chronic, crippling conditions with a prevalence of fewer than one per 1,000 people. These include certain endemic infectious diseases with very low frequency, inherited malignancies, congenital deformities, and autoimmune disorders [7].

Orphan Diseases in India

Regarding the Indian situation, over 450 rare illnesses have been found there to date. Statistics from the 2011 national population census were released, and it was calculated that 72,611,605 people in India were predicted to have rare diseases and disorders. Nowadays, there is a rise in awareness of rare diseases [8,9]. Although genetic testing has revealed that cystic fibrosis is common in India, the condition was previously believed to be extremely rare. According to reports, the population of India is more affected by rare diseases than the global average, but government initiatives are still scarce, and the country does not have any national laws about rare diseases or orphan medications [10,11].

Recently on January 13, 2020, a draft National Policy for Rare Diseases in India was released by an expert group appointed by the Ministry of Health and Family Welfare. The policy was finalized in 2021. This strategy does

not use prevalence for classification; instead, it uses the disease's location, degree of rarity, and suitability for a clinical trial [12]. Rare disease research is a complicated and diverse field. New rare diseases and conditions are frequently discovered and documented in medical literature, resulting in a continually shifting landscape for uncommon diseases. This is still a young discipline, except for a few rare disorders, where great strides have been made. For a very long time, there was no meaningful study or public health policy addressing concerns relating to the subject of uncommon diseases, and clinicians, researchers, and policymakers were entirely unaware of them. This presents significant obstacles to the creation of an all-encompassing policy on rare diseases. Nevertheless, it is critical to act now to address uncommon diseases holistically and thoroughly, both in the short and long terms [12]. Since 80 percent of orphan diseases have a hereditary basis, children are disproportionately affected [13]. Seventy percent of rare diseases begin in childhood, and about eighty percent are thought to have a genetic basis. [14] Approximately 9% of people in Southeast Asia are affected by them. One explanation for the high incidence of uncommon diseases in this area is thought to be the cultural practice of consanguineous marriages. [15]. Many rare diseases in India are also attributed to consanguinity in the south and endogamy in the north. [16]. Determining the precise prevalence of uncommon diseases in India is challenging due to the lack of a consistent definition. However, the approximate number of Indians suffering from uncommon diseases is between 72 and 96 million. [17]. The National Registry for Rare Diseases, which is run by the Indian Council of Medical Research (ICMR), compiles epidemiological data about rare diseases. There were 4,001 rare diseases identified as of October 31, 2021; [18] the most prevalent ones are sickle cell anemia, hemophilia, thalassemia, autoimmune diseases, primary immune deficiencies in children, lysosomal storage disorders (like Pompe disease), Hirschsprung disease, Gaucher's disease, Cystic Fibrosis, Hemangioma, and certain types of muscular dystrophy. [17]. Identified genetic roots account for 80% of uncommon disorders. There are also uncommon illnesses that arise from allergies, bacterial or viral infections, or degenerative and proliferative elements [19]. Based on their clinical experience, the experts have determined and categorized the following kinds of disorders for this policy [12]:

Group 1: Disorders amenable to one-time curative treatment:

a) Disorders amenable to treatment with Hematopoietic Stem Cell Transplantation (HSCT) –

I. Lysosomal Storage Disorders (LSDs) for which Enzyme Replacement Therapy (ERT) is presently not available and severe forms of Mucopolysaccharidosis (MPS) type I within the first 2 years of age.

II. Adrenoleukodystrophy (early stages), before the onset of hard neurological signs.

III. Immune deficiency disorders like Severe Combined Immunodeficiency (SCID), Chronic Granulomatous disease, Wiskot Aldrich Syndrome, etc.

b) Disorders amenable to organ transplantation

i. Liver Transplantation -Metabolic Liver Diseases:

a. Tyrosinemia,
b. Glycogen storage disorders (GSD) I, III, and IV due to poor metabolic control, multiple liver adenomas, or high risk for Hepatocellular carcinoma or evidence of substantial cirrhosis or liver dysfunction or progressive liver failure,
c. MSUD (Maple Syrup Urine Disease),

ii. Renal Transplantation-

a. Fabry disease
b. Autosomal recessive Polycystic Kidney Disease (ARPKD),
c. Autosomal dominant Polycystic Kidney Disease (ADPKD) etc.

iii. Patients requiring combined liver and kidney transplants can also be considered if the same ceiling of funds is maintained. (Rarely Methyl Malonicaciduria may require a combined liver & Kidney transplant) etc.

Group 2: Diseases requiring long-term/lifelong treatment having relatively lower costs of treatment and benefits have been documented in the literature and annual or more frequent surveillance is required:

a) Disorders managed with special dietary formulae or Food for special medical purposes (FSMP)
   i) Phenylketonuria (PKU)
   ii) Non-PKU hyperphenylalaninemia conditions
   iii) Maple Syrup Urine Disease (MSUD)
   iv) Tyrosinemia type 1 and 2
   v) Homocystinuria

b) Disorders that are amenable to other forms of therapy (hormone/ specific drugs)

i. NTBC for Tyrosinemia Type 1
ii. Osteogenes isImperfecta – Bisphosphonates therapy
iii. Growth Hormone therapy for proven GH deficiency, Prader Willi Syndrome, Turner syndrome, and Noonan syndrome.

Group 3: Diseases for which definitive treatment is available but challenges are to make optimal patient selection for benefit, very high cost, and lifelong therapy.

3. a) Based on the literature sufficient evidence for long-term outcomes exists for the following disorders

1. Gaucher Disease (Type I & III {without significant neurological impairment})
2. Hurler Syndrome [Mucopolysaccharisosis (MPS) Type I] (attenuated forms)
3. Hunter syndrome (MPS II) (attenuated form)
4. Pompe Disease
5. Fabry Disease diagnosed before significant end organ damage.

3 b) For the following disorders for which the cost of treatment is very high and either long-term follow-up literature is awaited or has been done on a small number of patients

1. Cystic Fibrosis (Potentiators)
2. Duchenne Muscular Dystrophy (Antesensce oligoneucletides, PTC)
3. Spinal Muscular Atrophy (Antisense oligonucleotides both intravenous & oral & gene therapy)
4. Wolman Disease

Orphan Drugs

An orphan medicine is any medication created to treat a condition classified as "Orphan or Rare disease." These are developed in response to public health needs rather than by the pharmaceutical industry for commercial gain. Any pharmaceutical business that wants to develop an orphan medicine has significant challenges due to the high cost of research and development and the low return on investment [5]. Orphan medications provide a challenge to the medical community and are a significant public health concern.

Challenges in the diagnosis and treatment of rare diseases

Several issues make it difficult to diagnose uncommon diseases early on, such as inadequate screening and diagnostic facilities, a lack of understanding among primary care physicians, and others. Rare diseases are poorly understood by both the general population and the medical community. To accurately and promptly diagnose and treat these illnesses, many clinicians do not have the necessary knowledge and training. The fact that relatively little is known about the pathophysiology or natural history of most uncommon diseases presents a basic obstacle for research and development efforts in these areas. The majority of rare diseases still lack safe or effective treatments, despite recent advancements. As a result, a treatment for the uncommon illness might not be available even when a proper diagnosis is made [12].

Less than 1 in 10 patients receive disease-specific medication, and around 95% of uncommon diseases lack an approved treatment. When medications are accessible, the cost is so high that they severely deplete available resources. uncommon diseases do not represent a sizable market for pharmaceutical companies to develop and commercialize medications for because there are few people with certain uncommon diseases. Because of this, treatments for uncommon diseases are referred to as "orphan drugs," and rare disorders themselves are known as "orphan diseases." Even in cases when medications for uncommon illnesses are produced, the expense of research and development is seemingly covered by the exorbitant prices [12].

Initiatives taken at different levels

Mobility has recently been observed in India concerning research on uncommon diseases. Numerous projects are underway, including ones

about regulations, academic institutions, nongovernmental organizations, and other relevant fields

CDSCO INITIATIVE: The CDSCO published a notice on July 3, 2014, by circular 12-01/14-DC pt. 47, regarding the waiver of clinical trial requirements for approval of new drugs in the Indian population for drugs that have already received approval outside of India. It stated that this waiver is only applicable to orphan drugs for rare diseases and drugs indicated for conditions and diseases for which there is no treatment. Pharma stakeholders and DCG(I) met again on May 4, 2016, to discuss ways to help patients with rare diseases afford medications. IDMA and OPPI were tasked with developing the Indian definition of a rare disease, JDC (ER) was assigned the task of updating the timeline for orphan drug approvals, and a separate cell was proposed to handle rare disease concerns, the potential for a separate pricing mechanism for orphan drugs, and the potential for custom duty exemption.

ICMR initiative: In collaboration with ICMR, AIIMS, JNU, and PRESIDE, the National Initiative for Rare Diseases (NIRD) was established. The decision was made to identify people with uncommon diseases in the initial stage. April 27, 2017, saw the inauguration of the "Indian rare disease registry." All uncommon and ultrarare diseases that are common in India are to be covered by this registry. The registry's goals are to identify patients with rare diseases and use that information to inform future research and policy formulation.

CSIR and IGIB initiative The "Genomics for Understanding Rare Diseases India Alliance Network (GUARDIAN)" project, funded by CSIR, has been carried out by IGIB, New Delhi, to bring together and understand novel genetic variations to achieve translational applications by both clinicians and basic science researchers.

JUDICIARY initiative The Delhi High Court ordered the government to complete a rare disease policy in November 2016. The Union Ministry of Health presented a draft of the policy to the Delhi High Court on May 25. The Center was ordered by the Delhi High Court to promptly put its National Policy for Treatment of Rare Diseases into effect.

Government of India policy: The goal of the policy is to reduce the incidence and prevalence of rare diseases through an integrated and comprehensive preventive strategy that includes raising public awareness, premarital, post-marital, pre- and post-conception screening, and counseling programs to avoid the birth of children with rare diseases. Additionally, the policy aims to provide patients with rare diseases who can benefit from one-time treatment or relatively inexpensive therapy with access to affordable health care, while also taking competing priorities and resource constraints into account [12].

Conclusion:

The Orphan Drug market is largely hindered by the lack of support and resources from the respective governments and the failure of the various policies in addition to the various disapprovals by the regulatory authorities. In India, Orphan Medical Products (OMPs) are not exempted from customs duties as a result of proper regulations and guidelines which have restricted their growth in the drug market. To conclude, there are several obstacles in the way of developing orphan drugs, from financial limitations to a lack of clinical data. Several strategic initiatives and actions are visible, such as mergers and acquisitions and partnerships between academic institutions and pharmaceutical companies to discover novel orphan medication compounds. With the potential to eventually capture a bigger portion of the pharmaceutical market, the orphan medication market appears well-positioned right now.

Reference

1. Gorini F, Coi A, Mezzasalma L, et al. Survival of patients with rare diseases: a population-based study in Tuscany (Italy). Orphanet J Rare Dis 2021; 16:275.
2. Population matters. Current world population, 2022. Available: https://populationmatters.org/population-numbers?gclid= EAIaIQobChMIjcjIlIO5-AIVA853Ch0PnwM_EAAYASAAEgIp7vD_BwE.
3. Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 2020;28:165–73.
4. Chan AYL, Chan VKY, Olsson S, et al. Access and unmet needs of orphan drugs in 194 countries and 6 areas: a global policy review with content analysis. Value Health 2020;23:1580–91.

5. Ramakrishna, G., Jyothi, B.M., Farhana, S.K., Manjunadham, K., Hemanth, S., Raja, Y. and Nagabhushanam, M.V., 2023. A REVIEW ON ORPHAN DRUGS-INDIAN PERSPECTIVE.
6. Blin, O., Lefebvre, M.N., Rascol, O. and Micallef, J., 2020. Orphan drug clinical development. *Therapies*, *75*(2), pp.141-147.
7. Viswanath Pingali, Neelima Das, "Rare Diseases Require Support Too", *Vikalpa: The Journal For Decision Makers* 46, no. 2 (2021).
8. Shaik Salman Basha, S. M. Shakeel, M. V. Nagabhushanam, D. Nagarjuna Reddy, Brahmaiah Bonthagarala, The Assessment of Current Regulatory Guidelines for Biosimilars- A Global Scenario, World Journal of Pharmaceutical Research, ISSN 2277– 7105, 6(1): 351-369 2017
9. Shakeel S.M., Shaik Salman Basha, M.V.Nagabhushanam, D.Nagarjuna Reddy, Brahmaiah Bonthagarala, Comparision of Regulatory Requirements for Generic Drugs Dossier Submission in the United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249–5738, November-December 2016; 6(6): 1-19.
10. Mohanty R, Barick U, Gowda A, Nair A, Mittal S, Patil A. Scope of patient registries for rare diseases in India. Int J Med Res Health Sci, 2016; 5: 58–61. [Google Scholar]
11. Saikiran Reddy D, Pramodkumar TM, Reddy Y, Sirisha K. Orphan regulations for orphan drug development in India. Asian J Pharm, 2014; 8: 130. [Google Scholar]
12. NATIONAL POLICY FOR Rare DISEASES,2021 mohfw: https://main.mohfw.gov.in/sites/default/files/Final%20NPRD%2C%202 02021. pdf. [Last accessed on 2021 May 11]
13. Ministry of Health and Family Welfare, *National Policy For Treatment Of Rare Diseases*, 2017.
14. National Health Portal of India, "Rare diseases".
15. Rajasimha H.K., Shirol P.B., Ramamoorthy P, Hegde M, Barde S, Chandru V, et al., "Organization for rare Diseases India (ORDI) – addressing the challenges and opportunities for the Indian rare diseases' community", *Genet Research* (2014).
16. Steph Yin, "In South Asian Social Castes, a Living Lab for Genetic Disease", *NY Times*, July 17, 2017
17. Ministry of Health and Family Welfare, *National Policy For Treatment Of Rare Diseases*, 2017.
18. Lok Sabha, "Treatment of Rare Diseases", December 10, 2021..
19. Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. Intractable Rare Dis Res, 2012; 1: 3–9.