Misconception and challenges of rare disease in research and development of orphan drugs



Neha Sisodiya*, Rakhi Khabiya, G. N. Darwhekar
Acropolis Institute of Pharmaceutical Education and Research, Indore
Email: neha@acropolis.edu.in

Abstract
Rare diseases are those diseases which affect quality of life of both patient and their families. The greatest concern of research and development of pharmaceutical industries is to develop the drug for such disease which is commonly called as orphan drugs. Rare diseases are not at all rarely occurring diseases. In developed countries like Europe and America 25-30 million of patients are suffering from rare diseases and there are about 4000-5000 different types of rare diseases. Several factors have created a challenge and burden on R&D and pharmaceutical industries for upshot of drugs for these diseases. But it's been a misconception that pharmaceutical industries are neglecting such rare diseases because of lack of understanding the mechanism of these diseases, unavailability of patients for clinical trial purpose, high investment in R&D. But the fact is that investment by industries on R&D for orphan drugs is rising day by day.

Keywords: Rare diseases, orphan drugs, R&D, misconception.

1. Introduction

Rare diseases are uncommon and generally don't occur in many patients. The signs and symptoms of these diseases are diversified varying from person to person and disease to disease. There above 8000 types of rare disease. It is been estimated that 350 million people throughout the globe are suffering from rare diseases and in India almost seven crore people are suffering from rare disease. In state of Karnataka alone 3-40 million people are suffering from rare diseases. Therefore, the need of sustainable improvement in treatment of rare diseases is priority for pharmaceutical industry to develop orphan drugs. The upshot of orphan drugs led to many misconceptions like pricing of drug, rarity of disease and its impact on healthcare system (1). The regulations for orphan drug were introduced in the year 2000 in Europe which further extended to Japan and other countries. Today there are about 1000 orphan drugs to cure rare diseases, due to which there is a tremendous increase in the expenditure of R&D and orphan medical products (2).

2. Misconceptions encountered

2.1 Price of orphan drugs

Commonly, it was assumed that price of orphan drugs is comparatively high than non-orphan drugs. Orphan drugs are categorised into four different categories (3):

- The oncology group includes drugs which are generally used in multiple cancers. As compared to others, oncology treatment of rare disease is higher but effective from clinical point of view. It covers 44% of orphan and rare disease drugs.
- The repurposed drug that are approved for common indication that are extended by rare disease indication. They are 10% of approved orphan and rare disease drugs.
- The second to market rare disease treatment which covers 16% of approved orphan drug.
- The first to market non-oncology drugs which cover 30% but are not used as standard of care due to less effectiveness.

In all the four categories, it is utmost difficult to determine the price of orphan drugs for rare disease. The average price of oncology category per cycle is 34,000 Euros. For non-oncology and repurposed category, it is between 16000-24000 Euros. 70% of orphan drugs have low price and only 30% are higher price for rare diseases (4).

2.2 Impact on healthcare budget

Due to high price of orphan drugs it has prominently impacted affordability for health care budget. To justify this, the budget impact in Europe is 1-4.6% for rare disease (5). Moreover, population treated for rare disease is more that affects affordability. Data shows that budget for rare disease will be 4-6 % only in the next 5 years (6). Healthcare managers have observed that orphan drugs with high price are a big challenge for healthcare budget (7). In this concern, the price of orphan oncology drug is lower than non-orphan oncology drugs, and the population is also small and constricted.

2.3 R&D investment

Lot of investment is needed in R&D of orphan drugs and returns are also favourable. The specific legislative investment decided by regulatory has made it possible to invest in R&D for orphan drug discovery (9). Most importantly the development of orphan drug is generally a lengthy process which requires lot of substantial investment. Other key constituents are overall capital, success of development, time & other cost apart from R&D (8).

2.4 Manufacturing cost

The manufacturing cost of orphan drugs is higher than non-orphan drugs. Manufacturing cost of orphan drug depends on R&D investment and there is no other criteria like for non-orphan drugs. Pharmaceutical industries make profit to reinvest in other new medicines. Major factors are financial investment that require bringing product into the market, treatment efficacy, budget among others. Final drug price depends on the negotiation with government bodies, wholesalers, insurers, etc.

2.5 Excessive financial return

Companies involved in manufacturing drugs for rare and orphan disease yield financial return due to high price of drug products. It is been estimated that within ten years 11% is recovered (10). If 100M$ is invested in R&D it will generate 618M$ after 10 years with 11-14% of return. According to regulation, industries investing in R&D and marketing of orphan drugs take valuable incentives (11) and the main focus must be on patent protection.

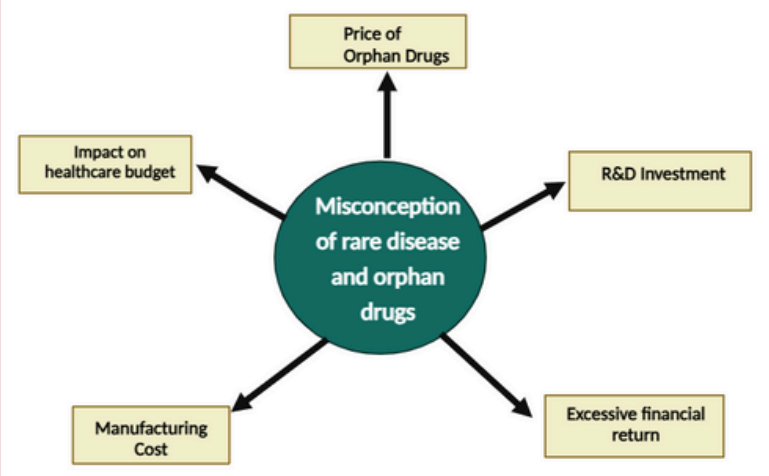

Figure 1. Misconceptions of rare disease and orphan drugs

3. Challenges of rare disease

The main challenge in rare disease is number of people affected by rare disease and their families suffering from undiagnosed cases, optimum care, lack of knowledge, unviability of physicians and improper guidelines.

3.1 Challenges to patient

The challenges faced by patient is finding proper physician to treat the disease, patients experiences on manifestation of disease, since they are unaware of conditions and its management. The price of drug available is a major challenge. Like in alpha 1- antitrypsin deficiency patients face lung dysfunction. Diagnosis is also delayed that increases the burden of rare disease and the available augmentation therapy is also very high.

3.2 Challenges to physicians

The management of rare disease is very difficult and major hurdle for physicians. The issue arises from unavailability of clear and accessible guidelines**.** Another challenge is geographical diversification of centres that provide treatment of rare disease which increase expenses of travelling.

3.3. Challenges to investigator

Investigators who are studying rare disease faces challenge in assembling cohorts of rare disease, availability of orphan drugs, funding for research and development (12).

4. Solution to these challenges

Patient advocacy organizations are working hard to provide optimal care to patients and families suffering from rare disease. Such organizations have collaborated with clinicians, physicians, government authorities, and pharmacist in building research. Examples of such organization are Alpha 1 Foundation, HHT Foundation, National Organization for Rare Diseases, Cystic Fibrosis Foundation, LAM Foundation. These foundations are focusing on finding cure of rare diseases. The success of these organizations hinges on fundraising support for research and development of orphan drugs. They also provide electronic consultancy and assist self-education of the patient on managing rare disease. Skype follow up are also available to patients through these organizations. Most importantly they provide funds for R&D. Example Orphan Drug Development Grant Program of Food and Drug Administration and Rare Disease Clinical Research Network for National Institute of Health (12-14).

5. Conclusion

Misconception regarding orphan drugs used for rare disease puts light on R&D, affordability and value of orphan drugs. Rare diseases are new concern to pharmaceutical industries and major challenge in exploring new treatment. For ensuring the success of rare disease R&D, it must appreciate and reward innovators. There are lots of misconceptions that are encountered regarding rare disease and orphan drugs related to manufacturing cost of drug, investment in R&D, impact on healthcare budget, price of orphan drugs, etc. But these all are misconceptions and the reality is far different because all these criteria are same for non-orphan drugs as well. There are various challenges faced by patients, physicians and investor like patients are unaware of disease, management of disease is difficult, manifestation of rare disease, etc. But patient advocacy organization is working towards resolving all the challenges by providing and collaborating with care association like government authorities, health sector, physicians, and clinicians.

References

1. Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nat Rev Drug Discov. 2010;9:921-929.
2. Rollet P, Lemoine A, Dunoyer M. Sustainable rare diseases business and drug access: no time for misconceptions. Orphanet J Rare Dis. 2013;8:109.
3. Wills Hughes W. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments. Orphanet J Rare Dis. 2012;7:74-10.
4. Country drug public list prices from: France: UK- National Health Service (NHS) via Drug Tariff; Chemist & Druggist. Official Journal of the French Republic (JORF), Germany- Informationsstelle für Arzneispezialitäten (IFA) via ABDATA, Italy- Italian Medicines Agency (AIFA) via Farmadati, Spain- Spanish Pharmaceutical Association (BOT). UK- National Health Service (NHS) via Drug Tariff; Chemist & Druggist
5. Schieppati A, Henter JI, Daina E, et al. Why rare diseases are an important medical and social issue. Lancet. 2008;371: 2039-41.
6. Schey C, " Estimating the budget impact of orphan medicines in Europe", 2010, 2020
7. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S: A comparative study of European rare disease and orphan drug markets. Health Policy. 2010;97:173-179.
8. Schieppati A, Henter JI, Daina E, et al.: Why rare diseases are an important medical and social issue. Lancet. 2008;371: 2039-2041.
9. Kiran N, Meekings," Orphan drug development: an economically viable strategy for biopharma R&D", Drug Discovery Today 2012
10. Jorge Mestre F, OHE report, "The R&D cost of a new medicine." 2012
11. Official Journal of the European Communities: (EC) No 141/2000 of the European parliament and of the council of 16 December 1999 on Orphan Medicinal products. Regulation. 2000, 1: 22
12. Stoller JK. The Challenge of Rare Diseases. Chest. 2018;153(6):1309-14.
13. Griggs RC, Batshaw M, Dunkle M. Clinical research for rare disease: opportunities, challenges, and solutions. Mol Genet Metab. 2009;96(1):20-26.
14. National Center for Advancing Translational Sciences, Rare Diseases Clinical Research Network. www.ncats.nih.gov. Accessed November 5, 2017.