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Mini Review

Rare Diseases and Orphan Drugs

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Abstract

The number of rare diseases, affecting approximately 350 million people around the world increases day by day while the desired success cannot be achieved in their diagnosis and treatment due to financial difficulties and ethical problems. However, the number of orphan drugs that provide treatment and whose research and development studies have been completed is not also increasing evenly. The equality of the healthcare services provided and the funds allocated to the orphan drug market by health authorities are still controversial. Even if all the needs of the individuals with rare diseases are met, the post-approval traceable data regarding the efficiency and safety of orphan drugs, which is critical for the individuals, is limited due to the small target population.

Keywords

Market access; Orphan drug, Rare disease; Regulation

Introduction

The prevalence of rare diseases is less than 1/200,000 in the USA and less than 1/2000 in Europe and they are usually untreated and have a high mortality rate [1]. Nearly 8000 rare diseases have been identified and dozens of rare diseases are identified each year [2].

Although the types of rare diseases vary according to population, they generally affect 10% of the population, for example, there are around 30 million diagnosed patients in Europe [3]. Nearly 80% of rare diseases are genetic and about half affect children [4].

Apart from all the difficulties in the treatment of rare diseases, the diagnosis is also difficult. The questionnaires show that 25% of patients wait 5-30 years for the correct diagnosis and 40% of the treatments is delayed due to misdiagnosis [5].

"Orphan" drugs are the drugs for very rare diseases which are aimed to be treated but in whose research and development the sponsors are unwilling to make investments since they have a very small market share that will not allow the sponsors pay off their capital invested in the research and development activities for the product. [6]

Materials and Methods

Rare Diseases

Rare diseases present challenges since they require a special approach and practices in diagnosis, treatment, and follow-up. It may take years to diagnose these diseases and therefore the disease may be neglected for many years. The patients consult to one doctor after the other to get a diagnosis and treatment. A survey carried out on 18,000 people in 17 European countries regarding eight rare diseases (Crohn's diseases, Cystic Fibrosis, Duchenne Muscular Dystrophy, Ehlers f Danlos, Marfan, Prader of Willi, Tuberous Sclerosis and Fragile X Syndrome) revealed that 25% of the patients waited 5-30 years for correct diagnosis and 40% of the patients were misdiagnosed before the correct diagnosis.6 16% of the patients underwent unnecessary surgical operations, 33% had unsuitable medical treatment, %10 received psychotherapy following psychosomatic pre-diagnosis; 25% of the patients went to another city and 2% to another country for diagnosis [5].

The ethics of research on rare diseases and their treatments are primarily related to the protection of the participant and the equality of healthcare provided. However, ethical details have not been very important in research. In researches, especially utilitarian and fair use principles are the most debated issues and a separate ethical rule applies in each case. Studies observ-

ing economic benefits are often considered to be unsuccessful particularly in terms of ethics. However, the standards used to set priority in healthcare services are inadequate due to the extreme uncertainty of the future benefits of investments in orphan drugs. Due to the limited market and low profitability of orphan drugs, their future benefits are also unclear, yet, investing in orphan drugs provides significant potential benefits for future generations. Therefore, the relevant non-governmental organizations always recommended that public policies by that set priorities with ethical reasons and provide adequate public funds should be determined [7].

Clear and transparent procedures are very important for the research and development of orphan drugs. Therefore, the competent health authorities should collaborate for rare diseases and orphan drugs, they should focus on global health research, improve their existing legislation for setting priorities and increase their funds [8].

At the same time, it is necessary to increase the flow of funds in order to create new and independent institutions at the international level and to encourage research [9]. Because existing organizations for rare diseases do not yet have political legitimacy like organizations for other diseases with global funds such as AIDS, tuberculosis and malaria [10].

Results

Orphan Drugs

Since drugs are materials that can eliminate the problems affecting human health and life when used correctly, that can end life when used incorrectly, they have an important role in human and community health [11]. The development of a new drug is a long, expensive and risky process. The decision of a company to make an investment to a certain therapeutic area depends on the difference between the expected income and the future costs (generally 5-7 years after the launch) rather than the current cash flow [12].

Orphan drug is the term referring to the drug used in the treatment of these diseases; since the number of patients is too low, investing in the research and development in this area or marketing these products is not profitable. Pharmaceutical companies generally neglect two drug categories: drugs for rare diseases and drugs for tropical diseases. Various authors and organizations (such as WHO) argue for consistent social interference and effective economic incentives to increase the R&D investments and further manufacture of these drugs due to the vital importance of the pharmaceuticals [4].

Since the manufacturers of prescription drugs can rarely profit from the marketing of drugs for such small patient groups, 25,000,000 Americans suffering from more than 6,000 rare diseases and conditions were denied access to effective drugs for many years. Prescription drug sector does not provide sufficient funds for the research regarding such treatments. The medication needs of developing countries are less than the increased demand for industrialized countries. Most of the pharmaceutical funds in developing countries are allocated to "profitable diseases" such as cancer, cardiovascular diseases, and nervous system diseases [13].

All these require the creation of certain incentives for the development and marketing of orphan drugs. These drugs are known as orphan drugs when they meet the identification criteria, and therefore they can use the incentives for development and marketing. Although a large number of the orphan drugs are approved by the authorities, approximately 10% of these drugs can be marketed [14].

Beyond the efficiency and safety problems of this problem, the biggest reason is the financial difficulties encountered in new drug development. Also, the reimbursement procedures for existing products on the market are also insufficient. The requirements for the inclusion of the drugs in reimbursement vary from country to country, delaying access of the patients to orphan drugs [15].

However, considering the prevalence of the diseases, most countries are still unable to plan significant changes regarding the assessment and marketing of orphan drugs [16].

In most European countries, drug prices are regulated by the relevant health authorities and the drugs are priced according to the assessments of the prices in reference countries; however, in some countries, prices are still 160% higher than those in the European country with lowest prices [17] [18].

Discussion and Conclusion

In recent years, orphan drugs approved by health authorities have some limitations: frequent lack of dosefinding studies, of controlled studies, of active comparator where available, of multicentre phase III trials with a suitable number of patients, insufficient exposure to the treatment, use of surrogate endpoints or weak proof of clinical benefit. The results of post-approval follow-up studies of orphan drugs approved for rare diseases take too many years. This delays the approval of future products. Since the effect of orphan drugs is evaluated on a small number of patients, it is harder to find more reliable methods. However, it is recommended that at least one phase II study be carried out to determine the clinical benefit of the treatment, even if there is a small number of patients. It should always be remembered that it is harder to determine the efficiency and safety of an orphan drug in a small population; because the adverse reactions occurring in rare diseases and their treatments will be much less than the number of patients using the drug. The lack of license applications for orphan drugs and the inadequacy of the submitted files is explained by the lack of funds. Creating a special fund for rare diseases and orphan drugs and providing assistance to researcher companies such as sponsorship and tax relief are urgent requirements. In contrast to the orphan drugs developed over the last 4 years, the number of which does not exceed doz-

ens, hundreds of rare diseases have been discovered, and this is a global health problem that cannot be overlooked. [19].

With the increase in drug development costs, drug developer companies often refrain from developing products for small patient populations. That is why treatments approved for rare diseases are called orphan drugs that cannot be developed economically by the pharmaceutical industry but meet the public health needs. Rare diseases are so rare that doctors do not see even one case in a year. There are of course positive developments regarding rare diseases and orphan drugs; however, 300 orphan drugs and devices approved in the last 25 years are still a drop in the ocean compared to thousands of rare diseases [20].

The determination of a rare disease and the orphan drug status is still a public issue in many countries and does not result in adequate successful breakthroughs due to the drug research and development economy. Moreover, there are no definite incentives even if diseases are life-threatening, and the expected sale of the medicinal product is unlikely to cover the investment. [21]. While drugs and vaccines for tropical diseases are defined, despite the fact that the number of rare diseases exceeds millions, the price of drugs can be too high to pay. [22].

Even if the prevalence of rare diseases is low, they are is observed in an average of 1/10 of the populations. A physician may encounter with someone with a rare disease maybe once or twice during his/her professional life. However, the disease will no more be rare when a relative is diagnosed with it.

Studies on rare diseases are increasing day by day. National and international incentives and funds are being created. Some patients who could not be treated in the past can now be treated and new drugs are discovered. However, many countries still do not have any regulations on orphan drugs and rare diseases, and there is not sufficient funding for rare diseases. National and more serious policies should be developed in this matter to achieve healthier outcomes and generations.

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