RARE DISEASES REPORT

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Rare diseases are chronic, progressive disorders that affect about 6–8% of the population. Almost 80% of rare diseases are of genetic origin. Globally between 6,000 and 8,000 rare diseases are described (www.eurodis.org), and every year three to four new diseases are added to the list. Most rare diseases emerge in the first years of life or in the childhood period. Patients and their families encounter problems such as delay in diagnosis, inadequate management of the disease as well as lack of information and resources.

The definition of rare disease differs in various regions of the world. The diseases which affect fewer than 200,000 (<80/100,000) patients in the USA and fewer than 50,000 patients in Japan are defined as a rare disease. On the other hand, the diseases that affect 1 out of 2,000 people in the European Union (EU) as well as in Turkey are being considered as 'rare diseases'. Moreover, while Behcet's disease, Thalassemia, Familial Mediterranean Fever are observed as rare diseases in most parts of the world, such diseases are more common in East Mediterranean Region including Turkey. The worldwide prevalence of rare diseases ranges between 5 and 60 individuals per 100,000 populations (on average 40/100,000, in Turkey 38/100,000). Thus, it is estimated that approximately 350 million individuals around the world and about 5 million individuals in Turkey have any type of rare disease.

Within rare diseases, a group of 'ultra-rare diseases (URDs)' are chronic disorders that are usually life-limiting and difficult to diagnose. Therefore, URDs have profound and devastating effects on patients and their families. The definition of URD differs according to several factors such as disease prevalence, the severity/effects of symptoms, curability, and genetic features of the disease. In European Union, the diseases that affect <2/100,000 individuals (<20 per million people) are described as URD. Inborn errors of metabolism represent a large group of URDs. This group of diseases affects 125/100,000 individuals as a whole. Globally 64 million individuals have URDs around the world; considering that consanguineous marriages are very common (22-24%) and families have many children in Turkey, it is assumed that there are approximately 30,300 individuals with URDs.

Only 5% of rare diseases have a cure. Since most of them have no cure, they are also called orphan diseases. It is necessary to get an accurate diagnosis of rare diseases not only for specific care and treatment but also for rational family planning. In this regard, 'next gene sequencing' technologies have been revolutionary developments that give hope to the patients due to providing a quick and inexpensive diagnosis. Unveiling molecular pathways of rare diseases play an essential role in comprehending molecular incidents involved in the pathogenesis of common diseases. In addition, in the last few years, international networks (e.g. the Orphanet Platform) have been established to seek the opinions of the world's leading experts to consult for accurate diagnosis and treatment of rare diseases. Individuals with rare diseases and their families have a great burden on the health system due to their special requirements. Like all patients, patients with rare diseases should be provided equal access to the health system in terms of clinical care, follow-up, and support systems.

Collecting data is indispensable for a better understanding of the causes of these diseases and for creating solutions (treatment, rehabilitation, support, and improving quality of life, etc.).

For this purpose, disease-specific registries and the establishment of biobanks for the collected samples and information are the priority issues.

Since most rare diseases do not have an effective medication, the development of personalized and innovative drugs for these causes a very costly and requires a long and difficult process. As it is well-known, drug development begins with a proof-of-concept procedure, followed by toxicological and preclinical animal testing. A series of clinical trials in humans are then conducted, from a group of healthy people to large patient groups, to evaluate the efficacy and safety of the candidate agent.

On the other hand, due to the nature of rare diseases, hardly patients can be included in clinical trials. The predominance of pediatric patients in this field and the complexity (heterogeneity) of the disease pose significant obstacles to clinical research. The traditional physician-based 'inclusion in clinical trials' approach is not sufficient in rare diseases, therefore, collaborations with patient associations should be used in case-finding. Owing to the aforementioned difficulties, regulatory bodies express some tolerance in applying existing standards in the approval (and licensing) process of drugs developed for rare diseases. In this regard, post-marketing clinical trials that can be conducted after the drug is approved for a certain rare disease may be a solution to gather pharmacovigilance data. Regulatory bodies in the US and Europe adopt similar approaches regarding post-authorization data collection requirements for rare diseases, repositioning of already in use drugs for common diseases, and orphan drug indications. In 2011, US Food and Drug Administration (FDA) and in 2015, the European Medicines Agency (EMA) published guidelines on this subject. Post-marketing observational, pragmatic and randomized-controlled clinical trials are conducted according to these guidelines. Observational studies cover both original data-collecting studies and secondary data use (retrospective studies). Original data collecting reduces the restriction caused by the limitations of retrospective studies. Disease registries focus on the details of a large group of patients with rare diseases. Clinical trial for a candidate drug, on the other hand, offers the health information associated with a single product. These researches may include the comparison of alternative treatments. Moreover, while designing the trials, it is necessary to consider the changes that may occur in the lifestyle of the patient related to the disease over time.

Despite all these difficulties, in the last few years the development of personalized (precious) medicines based on small molecules, antibodies, RNA, and gene therapy; also, thanks to technological innovations, promising results are offered for the treatment of even the most serious genetic diseases. However, such treatments are quite costly. Besides, it does not guarantee that a cure can be achieved in every case with these drugs. There are several factors that can affect the success of treatment. Therefore, it is inevitable for reimbursement institutions to act rationally in the access of patients to innovative drugs. The 'value-based care' approach, which aims to reduce the increasing treatment costs, the need for complementary insurance, or out-of-pocket expenses is increasingly gaining acceptance.

Mobile Health (M–Health) technologies may determine how clinical trials will be carried out in the future. The development of wearable devices, remote sensors, and mobile device applications is thought to help collect post-marketing data on the safety and efficacy of drugs. Tele-Health and Tele-Medicine technologies can be used for both providing education and counseling to patients and updating the physicians' knowledge.

The contributions of patient organizations to raise awareness of the society about rare diseases, the creation of the ‘Orphan Drug Law’ which leads to drug development worldwide, and finding patients for clinical research are undeniable. However, only half of these diseases have patient organizations around the world. These structures are even more scarce in Turkey.

In this report, current information on the genetic, epidemiological, and clinical features of certain rare diseases observed in Turkey is presented; it is also aimed to update knowledge of healthcare professionals on the treatments currently available for these diseases and the treatments being newly developed if any. Diseases due to inborn errors of metabolism are not described in detail in this report as they require a comprehensive assessment and are the subject of another document. Written in very plain language, this report has been prepared as a basic resource for the benefit of healthcare professionals in primary and secondary institutions. It can also be helpful for the patients and their relatives.