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Ethical and Social Aspects on Rare Diseases^{1,2}

32

Abstract: *Rare diseases are a heterogenic group of disorders with a little in common except of their rarity affecting by less than 5 : 10.000 people. In the world is registered about 6000-8000 rare diseases with 6–8% suffering population only in the European Union. In spite of rarity, they represent an important medical and social problem due to their incidence. For many rare diseases have no treatment, but if it exists and if started on time as being available to patients, there is a good prognosis for them to be able for normal life. The problems of patients affected by rare diseases are related to the lack of diagnosis and timely undergoing as well as their treatment or prevention. Orphan drugs are products intended for treatment, diagnosis or prevention of rare diseases, but for their development and marketing the industry has not been interested in yet because of their marketing reasons. Patients suffering from a rare disease although belonging to the vulnerable group for their specific health needs, is becoming invisible in the health care system due to their additional needs improperly recognized. Ethical problems faced by patients, but also health care professionals are related to the allocation of medical diagnostics, unequal approach to health care, inappropriately specialized social services as well as therapy and rare orphan drugs unavailability. Ethical questions related to clinical trails on orphan drugs, population screening and epidemiology testing on rare diseases will also be discussed in this paper.*

Key words: *rare diseases, patients' social problems, ethics, orphan drugs, drugs' availability.*

Introduction

In spite of the fact that there is no unique criterion for rare diseases, this term refers to any illness with the prevalence of 1: 2000 or less, while at the same time putting the patients in danger or disabling them chronically (on a national level the

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frequency could be different in relationship to the population size of the country). Two criteria are established for these diseases: there are no diseases which are so rare not to deserve proper attention or rare diseases are rare indeed, but patients with rare diseases are numerous. It is estimated that there are more than 5000 of such diseases, most of which are of genetic origin (almost all metabolic diseases belong to the group of rare diseases). These are permanent conditions, progressing constantly and their development is unpredictable. If they are diagnosed late and not treated on time, they may cause permanent disability or even death. However, if treatment is started on time, prognoses for a large number of rare diseases are positive and most patients may have a normal life. The treatment of rare diseases includes orphan medicinal products not developed commercially and usually expensive. Therefore, even though treatment may be available, it is practically unaffordable to all those who need it and limited to a small number of privileged, able to pay for it in highly developed Western countries.

Rare diseases are also referred to as “orphan” because none of the involved subjects show any interest in the patients suffering from these diseases. Health care policies and regulations do not recognise rare diseases as a public health threat as resources and technology in the area of health are limited and directed towards common diseases in larger populations. The pharmaceutical industry is not interested in research or development of new drugs in this area, whereas health services, i.e. professionals involved in the diagnosis and treatment of patients show a considerable lack of interest and an inadequate level of competency primarily due to insufficient knowledge about rare diseases and partially due to personal limitations related to the humane relationship and equal treatment of people suffering from rare diseases. Finding methods of treatment and taking care of patients suffering from rare diseases is an important public health care problem (Taruscio et al. 2010: 475).

33

This paper focuses on shedding additional light on rare diseases from the aspect of ethically acceptable or unacceptable social consequences. In order to achieve this aim, the deliberation will concentrate on the following topics: (I) social problems of patients and their families in terms of marginalisation and insufficient access to health care, as well as ethical aspects related to problems in diagnosing these diseases (wrong diagnosis, delay in diagnosis, variable clinical picture and presence of some intercurrent illness); (II) a specific biomedical and social problem is reflected in the fact that many rare diseases are innate and hardly recognizable illnesses, affecting mostly children. In addition, for the majority of them, adequate treatment is missing and/or unavailable. Children represent an extremely sensitive group to be included in clinical drug trials, since they may be included only under special conditions when it is absolutely necessary; (III) numerous common ethical questions about rare diseases related to the integrity and distributive justice in the treatment of these illnesses are being analysed, along with

related to biobanks of biological samples and the inclusion of vulnerable populations and risk groups in clinical trials of these drugs. Finally, a short overview of the problem of rare diseases in the Republic of Serbia is presented.

This is a descriptive research which includes two methods: (1) the method of document analysis of legal and ethical norms regarding the diagnosis and treatment of patients suffering from rare diseases and orphan medicinal products regulations; (2) a desk analysis of secondary data used in studying social problems of patients and their families.

The meaning and explanation of the term „rare“

34

According to the EU Committee of experts on rare diseases, the term rare disease refers to any illness life-threatening for patients or chronically disabling them, occurring with a frequency of 1:2000, i.e. affecting less than 5:10,000 people. Also, within the same group of rare diseases, there are those that are “very rare”, and, according to the World Health Organization, they influence one person in 100,000 of citizens or even less. Those patients are especially isolated and vulnerable (Dennis et al. 2010: 173; European Commission (EC) 2000 a, 2000 b, EC 2003). According to the definition given by the Orphan Drug Act and the U.S. Food and Drugs Agency, those are diseases with estimated prevalence of 1 case in 1,250 people (Remuzi and Garattini 2008: 1978). The lack of a unique International Disease Classification (IDC) precludes the implementation of a system for registering patients suffering from these diseases in the world. The European Commission Expert Group for Health and Consumer Protection has formed a working group for cooperation with the World Health Organization in order to provide a unique classification of rare diseases. It is necessary to establish a unique, universal system for registering patients suffering from rare diseases, both in national and international databases. Associations of citizens suffering from these diseases usually take the initiative to start national and international registries (Rubinstein et al. 2010: 394; Taruscio et al 2010: 475).

Bearing in mind the relativity of the term “rare”, even in medical literature, it can be assumed that the number of patients at a global level is high enough to be considered a Public Health priority and important public health problem influencing both developed and less developed countries because there is no rule according to which certain rare diseases affect some population or social group more than another (Schieppati et al. 2008: 2039). The EU Committee of experts on rare diseases estimates that 6–8% of the total world population have some rare disease, which means that about 30 million Europeans and 25 million people in the USA suffer from rare diseases. It is estimated that there are more than 5,000 of these diseases while some data show that 6,000 to 8,000 rare diseases are registered, but not yet fully confirmed in a medical sense, i.e. identified. Only 1,200 of them are

examined in detail and most of them are oncologic and metabolic diseases while the genetic origin has been identified for only 80% of rare diseases. They can be inherited or derived from new genetic mutations or from chromosomal abnormalities. They affect from 3–4% of births. Other rare diseases are caused by infections (bacterial or viral), resulting from allergies or chemical and radioactive influences, or even a combination of genetic and environmental factors. However, for most rare diseases, etiological mechanisms remain unknown due to the lack of scientific research (Barera and Galindo 2010: 493; Rubestein et al. 2010: 394). The lack of a unique International Classification of Diseases (ICD) prevents the establishing of a system for registering patients suffering from these illnesses in the world. Phenylketonuria, different types of leukaemia, epidermolysis bullosa, Fragile-X syndrome, cystic fibrosis, certain types of sterility, Crohn's, Wilson's, Fabry's, Gaucher's disease, are only some of the diseases referred to as "rare" (Eurordis, Internet; Norbs, Internet)

Rare diseases are permanent progressive illnesses and their development is unpredictable. If they are not diagnosed and treated on time, they may cause permanent disability or even death. A particular social and ethical problem lies in the fact that many of those diseases are innate and hard to detect, usually affecting children and for some of them there is no adequate treatment. There are rare diseases which cannot be treated but there are also those that can be treated. If a treatment is available and started on time, prognoses for a large number of rare diseases are positive and most patients may have a normal life. As such, rare diseases are a good example of social influence that patient associations, especially regional ones, may have on raising public awareness of the specific problems, and the significance of finding solutions through international and national regulatory procedures. Due to the activities of patient associations dedicated to improving the quality of life of all people that live with rare diseases, public awareness of rare diseases is enhanced and new methods for overcoming some of the ethical and social problems are found (Ayme et al. 2008: 2048). Eurordis is a European association of national patient organisations in the European Union. Since it was founded in 1997 with the aim to improve the quality of life of the patients suffering from various kinds of rare diseases, the awareness of rare diseases as medical, social and bioethical problem is significantly strengthened (Ingelfinger, Jeffrey 2011; Schieppati et al. 2008: 2039; Remuzzi and Garattini 2008: 1978; Eurordis, Internet).

Not only patient associations, but also researchers, pharmaceutical companies, health policymakers and regulators should deal with the problem of rare diseases, in order to discover new methods for preventing social marginalisation of patients. The founding of the National Organisation for Rare Diseases of Serbia (NORBS) in 2010 and its activities are a good sign that health policy creators will adequately address and treat the problems of rare diseases in the future (Ayme et al. 2008: 2048; Schieppati et al. 2008: 2039; Norbs, Internet; Eurordis, Internet).

Social problems of patients and their families

In diseases that not only cause disability, but are also life-threatening, there are problems regarding diagnosis and occurring due to wrong diagnoses or delay in disease detection, as well as in the variable clinical picture and/or presence of some intercurrent illnesses that may interfere with other socio-psychological problems (Barera and Galindo 2010: 493; Kole and Francois 2010: 223).

According to one of the three Eurordis research projects conducted in 24 European countries including only 18 rare diseases, “patients suffering from rare diseases are faced with the lack of access to correct diagnosis, delay in diagnosis, lack of information and public awareness, lack of scientific knowledge and expertise in tracking the development of a disease, lack of research, lack of treatment development, lack of appropriate quality healthcare, high costs for most of the few existing drugs, inequities and difficulties in access to treatment and care and the lack of professional social services” (Bignami 2007).

36

It is estimated that developed countries need approximately 4 to 6 years for diagnosing some rare disease, and in some cases, it lasts extremely long, even up to 20 years. Undeveloped countries need far more time and most of these diseases are not even diagnosed because there is no access to expensive modern diagnostic equipment needed for an accurate and precise diagnosis of a disease (Barera and Galindo 2010: 493; Fernandes 2007: 297). The absence of correct diagnosis may lead to the following problems in patients and their families: guilt, self-accusation, divorce, reduced professional opportunities, financial deprivation of the family, social isolation and marginalization and stigmatization as well. Excluded from the social community, these people and their families become “invisible” to society. It often happens that, in the case of undiagnosed genetic diseases, the husband blames his wife for transferring the illness to the child and vice versa. It is important to point out that in recessive illnesses, where both partners are carriers of the genetic “error” causing the illness, an adequate diagnosis often helps to improve the marital relations (Russell 1998: S4; Scjieppati et al. 2008: 2039; Remuzzi and Garattini 2008: 1978).

Another characteristic of undiagnosed disease is self-accusation. It often happens that parents of a child suffering from diagnosed rare disease are trying to talk to the doctor in private in order to find an answer to the question whether alcohol consumption, a venereal disease that one of the parents had during their lifetime, drug consumption or any other completely random factor caused the illness. In a large number of cases, diagnosed recessive disease is a relief for both parents because each of them, without any reason, blamed themselves for the child’s illness.

Considering that most rare diseases lead to disability of the patient, in a family where a child has a rare disease, only one parent can work, whereas the other one

has to stay at home and take care of the child. As a consequence, incomes are usually lower in comparison to other couples, which is an additional problem since the costs of care for this type of patient are very high. That is why the birth of a child with a rare disease usually leads to divorce as one of the parents, usually the father, leaves the house and passes the responsibility for the sick child on to the mother.

In a family where a child has a rare disease, parents usually do not leave the care of their child to another person, such as a friend, babysitter or even a healthcare worker, fearing that they will not take proper care of the child. Many of these parents are usually socially inactive, isolated from their friends or, in some cases, rejected by friends as they often prefer staying home and taking care of the child to going out and socialising. Tremendous pain that patients and their families are coping with is usually intensified by the lack of professional support in everyday life. European research of diagnosis and approach to health system services and social welfare departments in 20 European countries revealed that 59% of participants declared they had to either decrease or quit their professional activities because of the disease they themselves have or due to the obligation of taking care of relatives suffering from a rare disease. Approximately 16% of patients were forced to move because of an illness. One out of 5 patients was neglected by healthcare workers because of an illness (Eurordis, Internet).

37

In the cases of genetic diseases or undiagnosed diseases, close relatives can find it difficult to step into marriage because their partner may fear the child might suffer from a hereditary disease. It is not uncommon that a family is being socially discriminated because of the prejudice of the child carrying an illness not actually contagious, such in the case of some skin diseases which look as if infectious even though they are not. All of these underline the significance of determining the correct diagnosis, types of inheritance, risks and opportunities for this patient and their social inclusion (Geerly 2001: 785; Ethics committee (EC) 2005; Barera and Galindo 2010: 493; Rubinsteing et al. 2010: 394; Russel 1998: S4).

Despite the fact that there is no cure for the majority of these diseases, the quality of life of patients suffering from rare diseases and their families does not depend on the severity of the disease, but on the availability of treatment, health support services as well as broader social support (Rajmil et al. 2010: 251). Most of them are not recognised by the healthcare system, even though their health protection is legally regulated. Patients suffering from rare diseases should receive healthcare benefits in order to extend their life expectancy and improve their health. The quality of patients' life suffering from rare diseases is often reduced due to the lack or loss of independence. Even though the number of patients suffering from certain rare diseases is smaller, all patients together form a group of people for which the society has the moral obligation of distributive justice (Taruscio et al.

2010:475; Kole and Francois 2010: 223; Fernandez 2007: 297; Cookson and Dolan 2000: 323). the following is in the Charter of Fundamental Rights³, ratified by EU Member States, as part of the European Statute: “everyone has the right of access to preventive healthcare and the benefit of treatment under the conditions established by national laws and practice” (World Health Organization (WHO) 2003; The Charter of Fundamental Rights of the European Union, 2000).

38

In the European Union, during the past two decades, the awareness of problems regarding rare diseases and diagnoses, treatment and care have been improved significantly. The European Commission Expert Group for Health and Consumer Protection has formed a working group for cooperation with the World Health Organization in order to provide a unique classification of rare diseases. The European organizations Eurordis and Orphanet promoted the network of referral centres for rare diseases (Eurordis, internet; Orphanet, Internet; Taruscio et al. 2010: 475). Recommendations regarding joint activities in fighting rare diseases, which are not obligatory, but are adopted by the majority of Member States, include the following: the constitution of European referral centres for rare diseases, the improvement of visibility of rare diseases via the Orphanet data base, the improvement of rare disease classification and the constitution of the international classification of rare diseases as well as the joint expanding of the knowledge about rare diseases in Europe.

Regulatory demands related to rare diseases and availability of orphan medicinal products

The first country to pass the Orphan Drug Act in 1983 was the USA, followed by Japan in 1993, and eventually the European Union in 2000 (European Parliament and the Council of the European Union, Commission Regulation (EC) 2000 a; EC 2000 b; EC 2000 c). Drugs used in treating rare diseases are called orphan medicinal products. They may be defined as medicinal products intended for diagnosis, prevention and treatment of rare diseases, but their development is not supported by the pharmaceutical industry due to the economical reasons. They are referred to as “orphan” because, under normal market conditions, the development and marketing of drugs intended for treatment of a small number of patients suffering from rare diseases is not cost-effective for the pharmaceutical industry.

Orphan medicinal products may be:

- 1) Drugs intended for diagnosis, prevention or treatment of a specific rare disease, developed for treating patients suffering from very severe disease for which there is not any or only one satisfactory treatment.

³ The right to healthcare protection Article 2-95.

- 2) Drugs withdrawn from the market due to some economic or safety reasons but found to be useful for a rare disease or condition (for instance, a few decades ago Thalidomide, which belongs to the group of hypnotics, was withdrawn from the market because it appeared to be highly teratogenic. However, this drug turned out to have a good analgetic influence on particular diseases (leprosy and lupus erythematosus).
- 3) Drugs that include indications for other than a rare disease or condition.
- 4) Drugs obtained through processes of biotechnology and the cloning of genes used for derivation of biologically active peptides and proteins.

Regulatory agencies of particular countries and the European Medicines Agency (EMA) in Europe constantly direct their efforts to boosting the orphan drug development, both on national and European levels. Furthermore, the price of these drugs is high and they are unevenly accessible in EU, because the marketing authorisation of a product does not necessarily mean that product is launched immediately by the market authorisation holder in all Member States, and available to patients without unacceptable financial and administrative hurdles.

39

Orphan drug legislation differs from country to country which is why the distribution of these products is regulated differently in every country (European Parliament and the Council of the European Union, Commission Regulation (EC) 2000 a; EC 2000 b; EC 2000 c, Haffner 1998: 93; Orphanet, Internet; Goozner 2004). Different approaches to orphan medicinal products in some countries of the European Union, as a consequence of different legal regulations are illustrated in Table 1. Accessibility is usually through general out-patient reimbursement systems (for example, inclusion of the orphan medicinal product in the country's positive list(s), national formulary or in the general reimbursement scheme), or through an in-patient system (for example, in a centre of expertise, or inclusion, of the medicine in a hospital formulary/positive list). In some countries, derogatory reimbursement procedures may be applied to obtain access to orphan medicinal products. It is also possible in countries for orphan medicinal products without market authorisation to be accessed via one or more of the following initiatives: a compassionate use procedure (in the case of drugs which have applied for market authorisation or which are undergoing clinical studies), an off-label use procedure (in the case of the prescription of an already authorised medicine for an unapproved indication, dose, mode of administration, age group), or on a named-patient basis (in the case of a drug without market authorisation, when a doctor or centre of expertise requests supply of a drug directly from a manufacturer for a specific patient under their direct responsibility. *Aymé 2012*)

Different measures have been introduced to support research into orphan medicinal products by the countries worldwide.

Many countries provide funding for clinical research that tests the safety and efficacy of drugs, biologics, medical devices and medical foods in rare diseases or conditions. Improvement in drug accessibility depends on:

- Incentives given to the pharmaceutical and biotechnological industry to support research into orphan medicinal products.
- Incentives given for the development of *orphan medicinal products* including after the approval of the product
- The development of separate sectors within the pharmaceutical industry for *orphan medicinal products*' development and
- The broadening of knowledge about rare diseases, the improvement of communication and the cooperation between research centres, institutions, patients (Haffner 1998: 93; Orphanet, Internet, Gooyner 2004).

40

TABLE I. Some of the regulatory demands regarding rare diseases and drugs intended for treatment of rare diseases in some countries of the European Union and the Republic of Serbia (modified according to Denis et al. 2010: 173).

COUNTRY	BELGIUM	FRANCE	ITALY	THE NETHERLANDS	SWEDEN	GREAT BRITAIN	SERBIA
<i>Availability of national centres for rare diseases/ orphan medicinal products</i>	NO	YES	YES	YES	YES	YES	NO
<i>Health policy measures for facilitating drug development</i>	NO	YES	YES	YES	NO	NO	NO
<i>Encouragement of orphan drug research</i>	NO	YES	YES	YES	NO	NO	NO
<i>Availability of national procedures for drug marketing</i>	NO	YES	NO	NO	NO	NO	NO
<i>Procedure for drug use outside labelled indications (off-label use)</i>	NO	NO	YES	YES	NO	YES	NO
<i>Independent price formation for drugs</i>	—	—	—	—	YES	YES	NO
<i>Fixed price of drugs</i>	—	—	—	—	YES	YES	NO
<i>Social insurance of patients</i>	YES	YES	—	YES	YES	—	—

COUNTRY	BELGIUM	FRANCE	ITALY	THE NETHERLANDS	SWEDEN	GREAT BRITAIN	SERBIA
<i>Partial reimbursement of treatment</i>	NO	YES	—	YES	—	—	—
<i>Complete reimbursement of treatment</i>	YES	YES	YES	YES	YES	YES	—
<i>Drug distribution through hospital pharmacies</i>	YES	YES	YES	YES	YES	YES	YES
<i>Drug distribution through public pharmacies</i>	—	YES	YES	YES	YES	—	YES
<i>Prescription orphan drug procedures</i>	YES	YES	YES	YES	NO	YES	—

Ethical issues in clinical research regarding rare diseases

Unlike other diseases, rare diseases are hard to study. Thus it is extremely hard to even perform trials during the development of a new drug (Goozner 2004; Canadian Pediatric Society 2008; Helseth and Slettebo 2004: 298) because a small number of patients are involved in a clinical examination. Due to the insufficient number of patients suffering from rare diseases included in studies needed for obtaining an “orphan” drug in order to discover side effects occurring in only 1% of cases, crucial findings regarding the safety of these drugs are acquired through post-marketing studies (Buckley 2008: 2051). Some essential topics concerning the ethics of rare clinical examinations of orphan medicinal products and population-screening analyses of rare diseases will be discussed in this paper. Everyone is entitled to treatment and equal distribution of means intended for research and development of drugs which will improve the quality of life of patients suffering from rare diseases. Emphasis should be put on ethical issues regarding clinical researches of rare diseases that include children. These researches require a permit issued from the Ethics Committee and the participant’s compliance that a parent or legal guardian will provide for the child (Canadian Pediatric Society 2008; Council for International Organization of Medical sciences 2002; Helseth and Slettebo 2004: 298).

The principles of distributive justice and beneficence should have a decisive role in the process of determining the priorities of researches on drugs for rare diseases (Beauchamp and Childress 2001: 225).

Human genome research as well as the obtained results from it facilitate the improvement of the health of individual patients and human kind as a whole. At the same time, however, it indicates that in conducting this type of research, it is important to respect human dignity, freedom, human rights, whereby all the forms of discrimination on the basis of genetic features are explicitly banned (Greely 2001: 785; Cf. Arnason 2004: 11; WHO 2003; Kristinsson and Arnason 2007: 11; Hoeyer et al. 2004: 224). The implementation of genetics, not only in medicine and public health, but in rare diseases as well, becomes more important and it will be of huge importance in early detection, diagnosis and monitoring of various genetic diseases. Transplants, enzyme treatment and cell treatment are used either as a substitute for orphan medicinal products or in combination with them. These are quite expensive health technologies and their development requires many years of research. Manufacturing costs are very high because they require a high level of competence and expensive resources. Individual variations in drug responses are an important clinical problem and they range from the complete absence of reaction to a drug to various side effects. During the consumption of a particular drug, the reaction of the body to a drug will depend on the environment, the patient's diet, the overall health condition and genetic constitution of an individual. Studies in pharmacogenetics can have favourable or adverse effects depending on the genetic constitution of different individuals. The main goal of pharmacogenetics is to ensure that a drug is given to the patient who will benefit from that drug without causing side effects. The field of study regarding orphan medicinal product implementation is very important, and improvement of safety and treatment efficiency are essential. Doctors and pharmacists will have to broaden their knowledge in the field of pharmacogenetics in order to be able to analyse pharmacogenetic tests and properly prescribe treatment with pharmacogenetic drugs. New findings will impose additional responsibilities on health experts.

Rare Diseases in Serbia

According to data given by the National Organisation for Rare Diseases of Serbia (NORDS), between 480,000 and 640,000 citizens of Serbia suffer from some rare disease. Despite such a large number of patients, there is neither a national referral centre for detecting rare diseases nor a registry of drugs for rare diseases, not even a Register of Rare Diseases. In the Regulations of Conditions for the Import of Drugs and Medical Devices without Marketing Authorisation (Statute 2008) there is a list of 258 rare diseases in the Republic of Serbia. According to the Health Care Law, patients suffering from a rare disease fall under a very sensitive category within the group⁴ exposed to a higher risk of getting sick (Health Insurance Law, 2011). As of recently, the law specifies that the Minister of Health designates certain health institutions for referral for specific types of rare diseases. Implementation,

4 Healthcare Law, Article 11. Social Healthcare in the Republic of Serbia.

improvement and development of the activities and evaluation of the health promotion programme, primary, secondary and tertiary prevention and control of rare diseases is recognized by the Law of Public Health as a health branch of public interest (The Law of Public Health, 2009). New to the law is also that even patients suffering from rare diseases may acquire the status of an insurant in our country. In the organisation of NORDS, the “National Plan for Rare Diseases—real perspectives in the year 2012” was introduced on 30 November 2011 (NORBS, Internet). This plan underlines the necessity of defining a National Strategy and forming a National Registry of Rare Diseases, as well as the Rare Disease Fund within the Health Insurance Fund of the Republic of Serbia (the RFZO list). The government of Serbia has already approved the founding of a Fund for Rare Diseases of the Republic of Serbia. An additional problem lies in the fact that some drugs used in the treatment of rare diseases are still not registered in Serbia, and thus appropriate treatment is not available for such patients. Drugs used for treating some of the rare diseases are included in the list of medicines known as the “positive list” (list of medicines financed by the Health Insurance Fund of the Republic of Serbia—RFZO) in the Republic of Serbia. By comparing drugs under the international unlicensed names (INN) from the Lists of Orphan Drugs in Europe from January 2012 (Orphanet, 2012) with the Serbian National List of Medicines (RFZO list of medicinal products) from January 2012, 29 INN drugs from the Orphanet list were found in Serbian list, under 63 licensed names, as products of different manufacturers. As of January 2012, the RFZO List of Medicinal Products has 1969 registered medicinal products (licensed brand names). This means that of the drugs on the List, financed from the state health insurance fund, 2.3% may be used in treating rare diseases. The majority of drugs used for treating rare diseases registered on the RFZO List of Medicines belongs to List C (Drugs with a special regime of issuance), i.e. cytostatic drugs. Most rare diseases registered in Serbia are oncologic diseases, so it is not strange that the majority of drugs for treating rare diseases are completely covered by mandatory health insurance for this particular group of patients (RFZO, Health Insurance Law 2011, Statutes 2008, 2012,).

43

Due to the changes in the Health Insurance Law, it is determined that every individual suffering from a rare disease in Serbia may acquire the status of an insurant (Health Insurance Law, 2011) Due to the lack of availability or other procedures for obtaining these drugs, not only continuity, but also the quality of patients’ treatment suffering from a particular rare disease is questionable (Rajmil et al. 2010: 251).

Conclusion

Due to the lack of legal regulations on treating rare diseases in many countries in the world, patients and their families are directly faced with numerous obstacles when asking for professional help. Common problems of patients suffering from rare diseases are the lack of access to correct diagnosis, lack of quality information

and scientifically based knowledge of rare diseases, as well as the lack of appropriate healthcare, difficulties and inequities in access to essential, often new, health technologies. A rare disease is a heavy burden for the entire family, which is confronted with great difficulties in finding the appropriate treatment for the diseased member. A better approach to “orphan” drugs and the improvement of research as well as the development of these drugs will contribute to overcoming some of these biomedical problems, maintain and/or improve the quality of patients’ life. Social problems of patients and their families in terms of marginalization and discrimination not only in social relations but also in the field of health protection and care are recognized as priorities in all Member States of the European Union. At the moment, citizen associations are the only reminders of the community in Serbia in terms of raising public awareness and solving social problems of patients. They are also the initiators of changes in approaching numerous regulatory, biomedical, ethical and social issues regarding disease prevention and diagnosis, treatment and rehabilitation of patients. Due to current changes in the Healthcare Law, patients suffering from rare diseases are categorized as particularly sensitive social groups.

To conclude, drugs for some rare diseases are now registered on the positive list of the Republic of Serbia, but their number is extremely low in comparison to the number of registered rare diseases. However, the problem of drugs availability for rare diseases is not present only in Serbia—it is a problem of the health funds and health systems in every country in the world, including the richest ones.

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References:

- “About Rare Diseases”, (internet) data accessible on: <http://www.Eurordis.Org>. (accessed June 27. 2011).
- Árnason, Gardar (2007), “On human genetic databases”, in Häyry Matti, Ruth Chadwick, Vilhjálmur Árnason, Garðar Árnason (eds.), *The Ethics and Governance of Human Genetic Databases: European Perspectives*. Cambridge: Cambridge University Press: 11–13.
- Arsić, Jasmina, Krajnović, Dušanka i Jocić Dragana (2012), „Znanja i stavovi farmaceuta o retkim bolestima i „orphan“ lekovima“, *Proceedings from the symposium „Health Outcomes & Social Pharmacy“*, Beograd: Univerzitet u Beogradu, Farmaceutski fakultet, str. 70–71.

- Aymé, Ségolène, Anna Kole, and Stephen Groft (2008), "Empowerment of patients: lessons from the rare diseases community", *Lancet*, 9629 (371): 2048–2051.
- Aymé Ségolène S., Charlotte Rodwell (eds.) (2012), "2012 Report on the State of the Art of Rare Disease Activities in Europe of the European Union Committee of Experts on Rare Diseases". (internet) data accessible on: <http://www.eucerd.eu/upload/file/Reports/2012ReportStateofArtRDActivities.pdf> (accessed on 2012, December 1).
- Barrera, Luis and Gilberto Cely Galindo (2010), "Ethical Aspects on Rare Diseases", in Manuel Posada de la Paz, Manuel and Stefen Groft (ed.), *Rare Diseases Epidemiology, Advances in Experimental Medicine and Biology* 686: 493–511.
- Beauchamp, Tom L. and James F. Childress (2001a), "Justice", in Tom L. Beauchamp and James F. Childress (ed.), *Principles of Biomedical Ethics*, New York: Oxford University Press: 225–282.
- Beauchamp, Tom L and James F Childress (2001b), "Beneficence", in Beauchamp, Tom L. and James F. Childress (ed.), *Principles of Biomedical Ethics*, New York: Oxford University Press: 165–224.
- Bignami, Fabrizia (2007), "Eurordis survey on orphan medicinal products availability in Europe", 6th Eurordis Round Table of Companies Workshop, Barcelona 9 July 2007. (internet) data accessible on: <http://www.eurordis.org/IMG/pdf/2007ODsurvey-eurordis.pdf> (accessed on 2011, December 1).
- Buckley, Brendan (2008), "Clinical trial of orphan medicines", *Lancet* 371: 2051–2055.
- Canadian Paediatric Society (2008), "Ethical issues in health research in children", *Paediatrics and Child Health*, 8 (13): 707–712.
- Cookson, Richard and Paul Dolan (2000), "Principles of justice in health care rationing", *Journal of Medical Ethics* 26: 323–329.
- Council for International Organizations of Medical Sciences (Cioms) (2002), "International ethical guidelines for biomedical research involving human subjects", *Bulletin of medical ethics* 182: 17–23.
- Denis, Alain with Lut Margaret, Christel Fostier, Irina Cleemput and Steven Simoens (2010), "A comparative study of European rare disease and orphan drug markets", *Health policy* 2–3 (97): 173–179.
- Ethics Committee of the Rare Disease Research Institute (2005), "Recommendations on the ethical aspects of population screening programmes for rare diseases", Strasbourg.
- European Commission (2000), Communication from the Commission on Regulation 2000/141/EC 2000 on orphan medicinal products, *Official Journal of the European Union* 2003; C178: 2.
- European Council (2000c), Charter of Fundamental Rights: the Presidents of the Commission, European Parliament and Council sign and solemnly proclaim the Charter in Strasbourg, *Official Journal of the European Communities*, C 364/01.
- European Parliament and the Council of the European Union, Regulation 1999/141/EC 16.12.1999. of the European Parliament and of the Council on orphan medicinal products, *Official Journal of the European Communities* 2000a; L18: 1–5.
- European Parliament and the Council of the European Union. Commission Regulation 2000/ 847/EC 27. 04. 2000. laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority", *Official Journal of the European Communities* 2000b; L103: 5–8.

- Eurordis, (internet) data accessible on : www.eurordis.org (accessed on 2011, December 1).
- Fernandez, Conard V. (2007), "Our moral obligations in caring for patients with orphan cancers", *Canadian Medical Association Journal* 3 (176): 297.
- Goozner, Merrill (2004), *The \$800m pill. The truth behind the cost of new drugs*. Berkeley: University of California Press.
- Greely, Henry T. (2001), "Informed consent and other ethical Issues in human population genetics", *Annual Review of Genetics* (35): 785–800.
- Haffner, Marlene (1998), "Orphan drug development—international program and study design issues", *Drug Information Journal* 32: 93–99.
- Helseth, Sølvi and Åshild Slettebø (2004), "Research involving children: some ethical issues", *Nursing Ethics* 11: 298–308.
- Hoeyer, Klaus, Bert-Ove Olofsson, Tom Mjörndal, Niels Lynøe (2004), "Informed consent and biobanks: A population based study of attitudes towards tissue donation for genetic research", *Scandinavian Journal of Public Health* 32: 224–229.
- Ingelfinger, R Julie and Jeffrey M. Drazen (2011), "Patient Organizations and Research on Rare Diseases", *New England Journal of Medicine* 17: 1670–1671.
- 46 Kemp, Peter, and Rendtorff D. Jacob (2008), "The Barcelona Declaration", *Synthesis Philosophica* 46(2): 239–251.
- Kole, Anna and François Faurisson (2010), "Rare diseases social epidemiology: analysis of inequalities", in M. Posada de la Paz, S.C. Groft (ed.), *Rare Diseases Epidemiology, Advances in Experimental Medicine and Biology* 686: 223–250.
- Kristinsson, Sigurður and Vilhjálmur, Árnason (2007), "Informed consent and human genetic database research", in Häyry Matti, Ruth Chadwick, Vilhjálmur Árnason, Garðar Árnason, (ed.), *The Ethics and Governance of Human Genetic Databases: European Perspectives*, Cambridge: Cambridge University Press: 199–216.
- "Lists of Orphan Drugs in Europe", Orphanet Report Series, *Orphan Drugs collection*, January 2012, (internet) data accessible on : http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf. (accessed on 2011, October 20).
- Norbs, (internet) data accessible on: <http://www.norbs.rs> (accessed on 2011, December 1).
- Orphanet, "What is an orphan drug?", (internet) data accessible on: http://www.orpha.net/consor/cgi-bin/home_Info.php?PHPSESSID=c2c2ccf314be9c80bf3b40a695da bb36&file=MoDf (accessed on 2011, December 1).
- Rajmil, Luis, Lilisbeth Perestelo-Pérez and Michael Herdman (2010), "Quality of life and rare diseases", *Advances in experimental medicine and biology* 686: 251–272.
- Remuzzi, Giuseppe and Silvio Garattini (2008), "Rare diseases: what's next?", *Lancet* 9629 (371): 1978–1979.
- Rubinstein, Yaffa and Stephen Groft, Ronald Bartek, Kyle Brown, Ronald Christensen, Elaine Collier Amy Farber, Jenifer Farmer, John Ferguson, Christopher Forrest, Nicole Lockhart, Kate McCurdy, Helen Moore, Geraldine Pollen, Rachel Richesson, Vanessar Miller, Sara Hull, Jim Vaught (2010), "Creating a global rare disease patient registry linked to a rare diseases biorepository database: Rare Disease-HUB (RD-HUB)", *Contemporary clinical trials* 5 (31): 394–404.
- „Pravilnik o Listi lekova koji se propisuju i izdaju na teret sredstava obaveznog zdravstvenog osiguranja“ *Službeni glasnik Republike Srbije* broj 83/2012 i 98/2012 („Rulebook on the list of drugs that are prescribed and dispensed at the expense of the

- mandatory health insurance“ *Official Gazette of Republic of Serbia*, Belgrade: No. 83/2012 and 98/2012).
- „Pravilnik o uslovima za uvoz lekova i medicinskih sredstava koji nemaju dozvolu za stavljanje u promet“ *Službeni glasnik Republike Srbije* br. 37/08 i 45/08 („Rules of conditions for the import of medicines and medical devices which do not have the marketing authorization“ *Official Gazette of Republic of Serbia*, No. 37/08 and 45/08).
- Russell, A James (1998), “Ethical considerations in disease management of amyotrophic lateral sclerosis: a cross-cultural, worldwide perspective”, *Journal of Neurology* 2 (245): S4–S6.
- Schieppati, Arrigo, Jan-Inge Henter, Erica Daina, and Anita Aperia (2008), “Why rare diseases are an important medical and social issue”, *Lancet* 9629 (371): 2039–2041.
- Taruscio, Domenica, Luciano Vitozzy and Rumen Stefanov (2010), “National plans and strategies on rare diseases in Europe”, *Advances in experimental medicine and biology* 686: 475–491.
- „Zakon o javnom zdravlju“, *Službeni glasnik Republike Srbije* broj 72/2009 („The Law on Public Health“ *Official Gazette of Republic of Serbia*, No 72/09)
- „Zakon o izmenama i dopunama Zakona o zdravstvenom osiguranju“ *Službeni glasnik Republike Srbije* broj 57/2011. („Law on Revisions of the Law on Health Insurance“ *Official Gazette of Republic of Serbia*, No 57/11)
- „Zakon o izmenama i dopunama Zakona o zdravstvenoj zaštiti“ *Službeni glasnik Republike Srbije* broj 57/2011. („Law on Revisions of the Health Care Law“ *Official Gazette of Republic of Serbia*, No 57/11)
- World Health Organization (2003), “Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights. European Partnership on Patients’ Rights and Citizens’ Empowerment”, Geneva: World Health Organisation: 3; (internet) data accessible on: <http://ww.codex.vr.se/texts/whofinalreport.rtf> (accessed on 2011, January 27).

Dusanka Krajnovic

O etičkim i društvenim aspektima retkih bolesti

Apstrakt

Retke bolesti su veoma heterogena grupa poremećaja i imaju malo toga zajedničkog osim retkosti, pošto pogađaju manje od pet osoba na 10.000 ljudi. U svetu je evidentirano između 6.000 i 8.000 retkih bolesti koje pogađaju šest do osam procenata stanovništva samo u Evropskoj uniji. Dakle, iako retke, one predstavljaju važan medicinski i socijalni problem s obzirom na broj obolelih. Za mnoge retke bolesti nema terapije, a ukoliko ona postoji i ako se na vreme započne i bude dostupna pacijentima, postoje dobri izgledi da će oboleli moći da žive normalnim životom. Problemi s kojima se susreću pacijenti sa retkim bolestima vezani su za dijagnostikovanje u smislu nemogućnosti ili nepravovremenog postavljanja dijagnoze, kao i same terapije ili prevencije pojave bolesti. Orphan lekovi su proizvodi koji su namenjeni za lečenje, dijagnozu ili prevenciju retkih bolesti, za čiji razvoj i marketing industrija nije zainteresovana iz tržišnih razloga. Pacijenti s retkim bolestima, iako pripadaju osetljivoj grupi, jer imaju specifične zdravstvene potrebe, ostaju nevidljivi u zdravstvenom sistemu, jer se njihove dodat-

ne specifične potrebe ne prepoznaju. Etički problemi s kojima se susreću pacijenti, ali i zdravstveni radnici, tiču se alokacije zdravstvene dijagnostike, nejednakog pristupa zdravstvenoj zaštiti i nezi, nedostatka specijalizovanih socijalnih usluga, kao i nepostojanja i nedostupnosti terapije orphan lekovima. Etička pitanja retkih kliničkih ispitivanja orphan lekova i populacionih i skrining ispitivanja u vezi sa retkim bolestima takođe su razmatrani u ovom radu.

Ključne reči retke bolesti, društveni problemi obolelih, etika, orphan lekovi, dostupnost lekova.