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Chapter

Pharmacotherapy of Rare Diseases in Serbia: The Current State of Art

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Abstract

Rare diseases affect less than 1 in 2000 or 5 in 10,000 people by definition. Most of those diseases have genetic basis (80% of cases) and first symptoms appear in early childhood (50% of cases). Most of these diseases are chronic and degenerative and pharmacotherapy is not available for many of them. Until today, there are more than 7000 rare diseases. In Serbia, the problem of diagnosis and pharmacotherapy of rare diseases is currently under public scrutiny. Patients who suffer from rare diseases in Serbia face many challenges in terms of awareness, timely diagnosis, and adequate treatment. These people are often misdiagnosed or the diagnosis is delayed due to several problems: lack of awareness among medical professionals, lack of expertise, unavailability and/or high costs of diagnostic tests, etc. According to the National Organization of Patients with Rare Diseases in Serbia (NORBS), many diagnostic procedures have to be conducted abroad and the process comprises many difficulties: high costs, travel expenses, or transportation of biological material. Although national legislation ensures the availability of drugs for those diseases, pharmacotherapy is faced with many problems. In this work, we aim to show that improvement of the knowledge regarding rare diseases among both professionals and patients represents a crucial step for enhancement of perspectives for those patients in our community.

Keywords: rare diseases, pharmacotherapy, physicians, patients, knowledge, attitudes

1. Introduction

A rare disease or an orphan disease represents any disease that affects a small percentage of the population. According to data from Europe, a disease or disorder is defined as rare when it affects less than 1 in 2000 citizens (there are so rare diseases that affect 1 person in 100,000 or even less) [1].

The most significant matters concerning rare diseases (RDs) are as follows: (1) these diseases are often chronic, progressive, degenerative, and life-threatening; (2) most of them (80%) have identified genetic base; (3) in the majority of cases (75%), the first symptoms appear in early childhood (30% of rare disease patients die before the age of 5); (4) RDs represent disabling conditions: they have

tremendous social and socio-economic impact on one country, because they affect not only the patients but also their families and the whole society.

It is estimated that more than 7000 rare diseases have been detected and described so far. European Organization for Rare Diseases (EURORDIS) represents a unique, non-profit alliance of rare disease patient organizations from 72 European countries. According to this organization, 30 million people in Europe suffer from some of the numerous rare diseases. A similar organization exists in Serbia (NORBS), which estimates that such patients are about half a million in our community [2].

Patients suffering from RDs are faced with numerous complications: deficit of public and scientific education of the diseases, delay in diagnosis (or lack of access to correct diagnosis), heavy social consequences (stigmatization, isolation, discrimination, reducing professional opportunities, etc.), lack of appropriate quality healthcare, high prices of these drugs and complicated procedures for their procurement, etc. [3]. Also, people affected with RDs may require other medicinal devices (diapers, special nutritional preparations, wheelchairs, etc.). The fact that these expenses are not reimbursed by the national health insurance represents additional problem in everyday life of these patients and their family. All these obstacles have led to many charitable actions aimed at collecting donations in order to improve treatment solutions as well as to involve media in raising public awareness of this topic [2, 3].

Although national legislation ensures the availability of drugs for those diseases, (“orphan drugs”), the National Register of RDs still does not exist in Serbia. It is important to know that there are hospital registries for some rare diseases but a systemic and universal approach is still missing. Additionally, most of these conditions are not coded in the ICD-10, which only has codes for 500 of the rare diseases [4].

Beside this, pharmacotherapy of rare diseases in our country is also challenged with many difficulties, not just due to legislative obstacles. Although there are not enough registered orphan drugs, many of them can be found on the “black” market, in private pharmacies at very high prices and without adequate supervision [5].

Serbia has made certain progress in the area, but numerous unresolved issues remain. It should be pointed out that the importance of this topic was recognized in our country for the first time few years ago, in 2014. At that moment, certain amendments displayed the need for the development of centers for rare diseases and also declared this group of patients as a special category with the right to use free health insurance. In addition, a special budget from the Ministry of Health was assigned to finance treatment with orphan drugs [6, 7].

In addition to the above, National Organization for Rare Diseases in Serbia (NORBS) represents a non-governmental, non-profit organization that was founded in 2010 with an aim to improve the quality of life for people affected with RDs in Serbia.

2. Rare diseases patients as vulnerable subjects in clinical trials: bioethical challenges

The particular question that arises here is related to bioethical aspects of pharmacotherapy of these diseases and all obstacles along the way of examination of special kind of drugs intended to treat small number of patients (the so-called orphan drugs).

The issue of ethical and bioethical aspects of experiments including humans (which was the forerunner of clinical trials) was almost completely ignored by medical ethics of the late nineteenth and early twentieth century. It is relevant to mention that the sensitivity toward medical research subjects belonging to

vulnerable groups was first expressed clearly in the Declaration of Helsinki (it was adopted by the 18th World Medical Association General Assembly in Helsinki in 1964, and revised several times (most recently in 2013) [8].

Generally, patients suffering from rare diseases could be considered as the members of vulnerable groups. As we already mentioned, most of these conditions are chronic, degenerative, and life-threatening, of unknown or genetic origin, and mainly affect children [2, 3]. Some of these diseases have a devastating impact on all aspects of the patients' lives and their careers. Additionally, the development and availability of drugs for RDs could challenge basic bioethical principles. Four commonly accepted principles of health care ethics, excerpted from *Beauchamp and Childress*, include the: (1) principle of respect for autonomy, (2) principle of non-maleficence, (3) principle of beneficence, and (4) principle of justice [9].

The first bioethical principle—respect for the autonomy of the patient—means that the patient has the capacity to act intentionally, with understanding, and without controlling influences that would mitigate against a free and voluntary act. This principle is the basis for the practice of “informed consent” in the physician/patient transaction regarding health care, which represents one of postulates of modern clinical trial. The principle of non-maleficence requires us, as medical professionals, to not intentionally create harm or injury to the patient, either through acts of commission or omission. The meaning of the Principle of Beneficence is that health care providers have a duty to be of benefit to the patient, as well as to take positive steps to prevent and to remove harm from the patient. Finally, justice in health care is usually defined as a form of fairness, or as Aristotle once said, “giving to each that which is his due.” [9].

In addition to the above, the utilitarian concept of bioethics could not be fully applied in this matter since it favors development of drugs for common disorders instead of the rare ones. One could argue that diseases are rare but there are a lot of patients suffering from them [5, 6]. These diseases represent a challenge not only for the individual and the family of the patient but also for the medical professionals, the entire health care system, and the complete society.

By considering the patients suffering from rare diseases as the members of vulnerable groups, we want to stress the presence of individualized medicine trend in contemporary medicine. Ethical declarations, codices, bioethical documents, and the function of the ethical committees were the indicators of individualizing medicine trend. Regarding the rare diseases issue, the indicators of individualizing medicine trend are certain documents: (1) EU Regulation on Orphan Medicinal Products (1999); (2) EU Regulation on Pediatric Drugs (2006); (3) Programme of Community Action in the Field of Public Health (2007–2013); and (4) EU 7th Framework Programme for Research (2007–2013) [8].

It can be concluded that above-mentioned case of “moving” from a random sample of hospitalized patients to specific group of patients, members of vulnerable groups, is the indicator of individualizing medicine trend and it continues to develop. One of its goals is certainly, we consider, the rare disease issue and the specific patient-physician encounter that includes the rare disease patient, namely, the patient *sui generis* as the subject of specific therapeutic research [8].

3. The aim of our study

Our research group deals with different aspects of rare diseases in our community: pharmacotherapy, bioethical issues, social significance, importance of education among medical students, patients, and professionals, etc.

In the first part of this work, we will briefly present the main results of the pilot study regarding pharmacotherapy of rare diseases conducted among physicians and clinical pharmacists who deal with these kinds of patients in Serbia.

In the next part of examination, we will present the main results of the survey conducted among patients suffering from rare diseases in our country.

4. The knowledge and attitudes of physicians and clinical pharmacists regarding pharmacotherapy of rare diseases in Serbia: a pilot study

In Serbia, clinical trials in the field of rare diseases are extremely rare and mainly relate to rare oncological diseases.

We considered that it would be important to examine the attitudes and knowledge of physicians and clinical pharmacists regarding the pharmacotherapy of rare diseases in Serbia. An anonymous pilot survey entitled “Attitudes of Physicians and Pharmacists Regarding Pharmacotherapy of rare diseases in Serbia” was designed and conducted by employees of the Department of Pharmacology, Clinical Pharmacology and Toxicology in a selected sample of subjects (N = 11, Internal Medicine Clinic and Central Pharmacy, KBC “Bezanijska Kosa” in Belgrade). The survey consisted of both open- and closed-ended questions. The attitudes of medical professionals were assessed by the 10-point Likert scale. The total response rate was 97.2%.

4.1 Physicians’ and pharmacists’ knowledge and attitudes concerning rare diseases: results

Our respondents found that the greatest problems of patients suffering from rare diseases in our environment are: lack of scientific knowledge (23%), complicated procedures for the procurement of drugs (21%), the lack of a sufficient number of registered medicines for these diseases (14%), etc. Although our examinees considered this issue as highly important in our country (on a scale of 0–10, our respondents gave an average score of 9), the majority of them (64%) assessed they were not sufficiently familiar with the existing legislation. According to our respondents, the treatment of patients with rare diseases in our environment can be improved: by forming a National Strategy for RDs (23%), raising general and professional awareness (20%), by creating a register of patients with rare diseases (20%), etc.

5. The knowledge and attitudes of patients suffering from rare diseases in Serbia

In the next part of our investigation, we performed a cross-sectional study for 5 weeks on outpatients and inpatients (Neurology Clinic, Department for Neuromuscular Disorders, Clinical Center of Serbia) who suffered from rare neurological diseases.

The anonymous questionnaire concerning the knowledge and attitudes of rare diseases and its pharmacotherapy was completed by a total of 60 patients (39 were male and 21 were female). The questionnaire consisted of both open- and closed-ended questions, and patients’ attitudes were assessed by the 10-point Likert scale.

All of our respondents suffered from different neurological diseases (myasthenia gravis, myotonic dystrophy, polyneuropathy, multiple sclerosis, syringomyelia, amyotrophic lateral sclerosis, etc.). The total response rate was 95.83%.

5.1 Patients' knowledge and attitudes concerning rare diseases: results

This part of our survey showed that slightly more than a third of participants knew the exact prevalence and definition of rare diseases in Europe. Although more than 70% of patients answered they knew what kind of disease is defined as “rare,” only half of the participants believed that they suffered from rare disease.

Our respondents found that dealing with this issue in our community is very important (median value: 9; interquartile range: 8–10), while availability of “orphan drugs” is still poor (median value: 2; interquartile range: 1–6).

The most important problems faced by patients suffering from rare diseases in Serbia include: lack of public and scientific knowledge (21.83% and 14.78%), insufficient number and cost of orphan drugs (14.08%), legislative obstacles (12.67%), delay in diagnosis and misdiagnosis (12.67%), etc.

It should be pointed out that only 16.6% of examined patients were part of some rare diseases patients' organizations and just a quarter of our respondents (26.6%) agreed to participate in clinical trials concerning orphan drugs.

According to our participants, the availability of drugs for RDs could be enhanced by the efforts of: the state (55%), medical doctors (30%), pharmaceutical companies and pharmacies (10%), rare diseases patients' organizations (3.33%), etc.

Finally, in order to improve the pharmacotherapy of RDs in our country, the examined participants suggested the following: well-timed diagnostics (25.78%), progress of the general awareness regarding this topic (22.64%), clarified orphan drug approval processes (16.9%), registration of more RDs drugs (11.3%), creating a RDs patients' register (7.6%), forming a National Strategy for RDs (6.2%), full implementation of legislation (4.7%), adequate control of orphan drugs available in private pharmacies in Serbia (4.25%), etc.

6. Discussion

In general, our questionnaires showed that the examined physicians and clinical pharmacists, as well as patients, were very interested in expressing their attitudes regarding the issue of rare diseases and their treatment in our country. This is confirmed by the high percentage of provided answers (the total response rate was 97.2% and 95.83%, respectively).

The first thing to notice here is that both the patients and medical professionals did not show sufficient knowledge regarding this topic. It is important to emphasize that both groups of our participants were directly involved in this issue (for survey, medical professionals who were in daily practice in contact with RDs patients and patients who belonged to the RDs patients' group by definition were selected).

Our respondents estimated the importance of rare diseases in our society as a problem of crucial importance. Here, we noticed a significant difference in attitudes between RDs patients and third- and sixth-year medical students that we have examined in previous research ($P < 0.01$). In opposite, the observed patients and examined students showed a similar opinion regarding the overall quality of health care of RDs patients, rated it as insufficient ($P < 0.05$) [10].

We need to reveal that the issue of pharmacotherapy of rare diseases involves different kind of ethical dilemmas and controversies. That is why we strongly believe that understanding and analyzing such a sensitive topic must also implement knowledge of basic principles of biomedical ethics [11–14].

In our survey, respondents found that the state was most responsible for the improvement of availability of orphan drugs. However, we need to be aware that national policies and activities of the state start from the initiative of those who

participate in the health system of one country (policy-makers, members of the regulatory bodies, medical doctors, pharmacists, patients, etc.). Our research has shown that patients do not participate sufficiently in these activities and do not take an active role in the fight to improve their position in society. Related to these findings, *Baker* and *Trisnadi* in their works emphasized the importance of understanding personal responsibility to address a bioethically vulnerable issue in one community [15, 16].

In the last three decades, the concept of “medicalization” of society (“a pill for every ill”) has been increasingly present in numerous bioethical debates [17]. In contrast to this phenomenon, there is a real need to develop novel drugs for rare diseases and their inaccessibility in many societies, on the one hand, and the lack of concern of the pharmaceutical industry regarding this topic, on the other [18, 19].

A controversial and substantive question would be is it reasonably and ethically justified to invest large amounts of money to treat a small number of patients? In a previous study performed on third- and sixth-year medical students, we received an affirmative answer to this question in both groups ($P < 0.05$) [10].

The most important results of survey conducted among third- and sixth-year medical students are shown in **Table 1**.

Finally, in order to improve the pharmacotherapy of rare diseases in Serbia, medical professionals and patients similarly suggested: improvement of general and scientific knowledge, well-timed diagnostics, simplified procedures for drug provision, registration of more appropriate drugs, etc. (see **Tables 2** and **3**).

The first comprehensive study was recently published by Joldic et al. related to the needs of patients with rare diseases in Serbia. According to this paper, four different groups of needs are identified: needs for health care, needs for social care, psychological needs, and other needs. The most important problems of RDs patients and their families arise first from the insufficient information and knowledge on this topic and second from the non-recognition of rare diseases in the legislation of health care system [7, 20–24].

The most important problems of patients (%)	Third year	Sixth year	P value
Lack of information in general public	67.71	56.61	<0.01
Lack of scientific knowledge	31.42	37.19	>0.05
Lack of access to correct diagnosis	46.28	42.56	>0.05
Lack of appropriate quality health care	49.71	40.08	<0.05
Lack of a sufficient number of registered drugs	41.43	70.24	<0.0001
Complicated procedures of drug provision	60.00	63.22	>0.05
High prices of drugs	86.29	80.58	>0.05
Other causes	2.00	1.65	>0.05
How to improve pharmacotherapy of rare diseases (%)			
Raise general awareness and expertise	30.57	60.00	<0.0001
Well-timed diagnostics	44.86	63.22	<0.0001
Simplified procedures for drug provision	50.00	70.66	<0.0001
Registration of more appropriate drugs	55.43	69.01	<0.01
The establishment of the National Plan for Rare Diseases	64.57	74.38	<0.05
Create the registry of rare diseases	54.58	53.72	>0.05

Bold values are represented statistically significant difference between groups.

Table 1.
Medical students' knowledge and attitudes concerning rare diseases.

The most important problems of patients (%)	
1. Lack of scientific knowledge	23
2. Complicated procedures for the procurement of drugs	21
3. Lack of a sufficient number of registered drugs for these diseases	14
4. Lack of access to correct diagnosis	12
5. Complicated procedures of drug provision	11
6. High prices of drugs	11
7. Other	8
How to improve pharmacotherapy of rare diseases (%)	
1. The establishment of the National Strategy for Rare Diseases	23
2. Raise general and professional awareness	20
3. Create registries of rare diseases	20
4. Well-timed diagnostics	18
5. Registration of more appropriate drugs	13
6. Other	6

Table 2.
 Physicians' and pharmacists' knowledge and attitudes concerning rare diseases.

The most important problems of patients %	
1. Lack of public knowledge	21.83
2. Lack of scientific knowledge	14.78
3. Lack of a sufficient number of registered drugs	14.08
4. Lack of access to correct diagnosis	12.67
5. Complicated procedures of drug provision	11.75
6. High prices of drugs	11.30
7. Unavailability of these drugs in private pharmacies	8.40
8. Other	5.19
How to improve pharmacotherapy of rare diseases %	
1. Well-timed diagnostics	25.78
2. Raise general awareness	22.64
3. Simplified procedures for drug provision	16.90
4. Registration of more appropriate drugs	11.30
5. Create registries of rare diseases	7.60
6. The establishment of the National Strategy for Rare Diseases	6.20
7. Full implementation of legislation	4.7
8. Other	4.88

Table 3.
 The knowledge and attitudes of patients suffering from rare diseases

7. Conclusions

We can conclude that our participants showed will to express their attitudes regarding this important medical, societal, and bioethical concern in our

community. Patients, as well as medical doctors and pharmacists, are aware of the most significant challenges concerning this topic in Serbia.

However, we need to improve both knowledge and attitudes of all participants in the health care system. Patients should be encouraged to more actively advocate for their rights through the formation of associations, and medical professionals to make greater efforts in the field of education on this subject.

Additionally, we believe that education is very important among medical students as future physicians, as our previous research has proven.

Finally, we would like to point out that at this moment our country has already conducted different kind of activities in order to create national strategy and registries of RDs, to form centers of expertise, to improve accessibility of orphan drugs, etc. Concerning this, we consider this is the critical point for conducting public discussion regarding this issue. An initiative like this should involve not just medical professionals and regulatory bodies, but the RDs patients and the general public as well. We strongly believe this is the unique way to significantly improve the position of these patients in our community in future.

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Conflict of interest

The authors declare no conflict of interest.

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