APŽVALGINIAI STRAIPSNIAI

Legal assessment of current situation on orphan patients in Lithuania

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Key words: *rare diseases; orphan patients; orphan medicinal products; legislation; patient rights.*

Summary. *After Lithuania joined the European Union, the Regulation (EC) No. 141/2000 on orphan medicinal products and Commission Regulation (EC) No. 847/2000 came into force as part of national legislation. Member States must adopt specific measures to increase knowledge on rare diseases and to improve their detection, diagnosis, and treatment.*

The aim of this article was to present and to assess the current legal situation on orphan patients and their treatment in Lithuania, to identify legislation gaps, and to propose some ideas how to facilitate the solution of the existing problems in this field.

For this purpose, European Union and Lithuanian legal documents on rare medicinal products are examined using a comparative method. With reference to inventory of Member States' incentives for rare diseases in national level, the most important issues, which orphan patients face to in Lithuania, are singled out.

In Lithuania, the situation of orphan patients in terms of protection of patient rights is insufficiently determined. The access to effective health care services or approved therapies in some cases is restricted. Working relationships between genetic services and various clinical specialists as well as with those in primary care are not legally determined; the number of clinical trials aimed at orphan medicinal products is low.

These results suggest a need for awareness raising among Lithuanian Government, health care specialists, patient organizations about the importance to improve practical implementation of European Union legislation and progressive experience of some European countries in this field.

Introduction

In recent decades, medicine and medical research have made remarkable progress ridding the world off a number of diseases. Nevertheless, there are still a great number of diseases, which cannot be treated satisfactorily and for which no medication or other diagnosis, prevention, or treatment is available. Patients with such diseases have been named the "health orphans" and the treatments that could cure them – "orphan medicinal products" (1). The label "orphan" arose largely because such drugs yield little financial return on investment because of the limited size of the rare disease drug market and therefore pharmaceutical companies have shown little interest in "adopting" treatments for rare diseases. (2)

Orphan medicinal product legislation was timely to address the unmet medical needs of patients suffering from rare diseases within European Union (EU), as they deserve access to the same quality of treatments as other patients. It is the result of an unwritten commitment between society (or at least governments representing the will of society) and the pharmaceutical industry to undertake research and development programs without return on investment in exchange for financial support and a period of market exclusivity (3). The legislation on orphan medicinal products is a part of a broader community policy to identify rare diseases as a priority area for action in the field of public health, which constitutes the area of common competence of EU and the Member States (4). Member States must adopt specific measures to increase knowledge on rare diseases and to improve their detection, diagnosis, and treatment.

In Lithuania, measures concerning rare diseases

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and conditions as well as the national incentives for rare medicinal products are insufficient yet. One of the reasons for such situation might be unawareness or disinterest of Lithuanian scientific community about the problem of rare diseases, despite of great international relevance of the problem. This caused another reason, which is related with little awareness of health care policy makers. Therefore, the aim of this article is to present and to assess the current legal situation on orphan patients and their treatment in Lithuania, to identify most important issues, which orphan patients face to. Some insights how to facilitate the solution of these problems are discussed.

For this purpose, European Union and Lithuanian legal documents on rare medicinal products are examined using comparative method. With reference to the inventory of Member States' incentive measures for rare diseases in national level (5), the most important issues which orphan patients face to in Lithuania are singled out.

Overview of the European regulation on orphan medicinal products

A European legal policy on rare disorders was effectively put into action with the Regulation 141/2000 (6) adopted on December 16, 1999, setting out a Community procedure for the designation of medicinal products and providing incentives for research, development and marketing of orphan medicinal products in the EU on the basis of United States experience.

On April 27, 2000, the Commission adopted a Regulation 847/2000 (7) laying down implementation rules and setting out the definitions essential for the application of Regulation 141/2000. As of April 28, 2000, the date this Regulation entered into force, sponsors/pharmaceutical companies have been able to submit applications for orphan medicinal product designation to the European Agency for the Evaluation of Medicinal Products (EMEA).

EMEA plays a major role, which was ascribed to it by Regulation 141/2000 in implementing orphan drug legislation, identifying those products eligible for incentives through a Community procedure for orphan designation (8). The designation is allowed based on epidemiological data (prevalence of rare disease ≤5/10 000), medical plausibility, and potential benefit (Reg. 141/2000, Art. 3) (6). Recognition of orphan drug status implies incentives for pharmaceutical companies to develop orphan medicinal products, including 10 years of market exclusivity in the EU once a marketing authorization has been granted, scientific advice to optimize development, guidance on preparing the dossier according to European regulatory requirements, direct access to EMEA centralized procedure for marketing authorization, fee reductions for all centralized activities including applications for marketing authorization, inspections, variations, and protocol assistance, and eligibility for grants from EU and Member States programs and initiatives supporting research and development (9, 6).

A major principle outlined by legislation of EU orphan medicinal products is that people affected by diseases treatable by orphan drugs must have the effective right to receive such treatment – patients with such conditions deserve the same quality, safety, and efficacy in medicinal products as other patients. This regulation couples the profit motive of interest of the pharmaceutical industry to the needs of the orphan patient. This supports important principles such as social justice and equality in society as a whole: individuals with rare disorders share the same desire and rights for effective treatments, which will relieve or remove their conditions, as those with common disorders (3, 10).

Between April 2000 and November 2007, about 700 applications for orphan designation were submitted to the EMEA with about 500 of them approved. Thirty-six of these products have gone on to receive marketing authorization through the centralized procedure (11).

National legal framework and rare diseases policy in Lithuania

After Lithuania joined the EU, the Regulation 141/2000 on orphan medicinal products and Commission Regulation 847/2000 came into force as part of national legislation. Furthermore, there are two main acts of national secondary legislation, regulating the accessibility of orphan medicinal products: Ministry of Health Decree (12) on the reimbursement of costs of treatment provided abroad, entered into force on January 16, 1999, and Decree of the State Patient Fund Directorate at the Ministry of Health, published on November 22, 2005 (12).

Reimbursement of treatment

Since the State's intervention in drugs matters aims to guarantee patients an effective use of the drugs administered to the by above mentioned secondary legislation, Lithuanian Government secures the access to the treatment, including orphan medicinal products for orphan patients by reimbursement from the fund earmarked for that purpose in the budget of the compulsory health insurance fund (12).

Patients get reimbursement for treatment of rare diseases and conditions on presenting specialist doctor's applications (reports). Applications must be approved by the Committee (consisting of 5 members) formed by the State Patient Fund (Art. 6) (13). Having a positive decision of the Committee, medical institution must take care of purchase of orphan medicines (Art. 29) (13). If orphan medicinal products were obtained in the absence of the approbation of the Committee or if they were purchased on patient's own resources, costs are not reimbursed (Art. 31) (13). In cases when a treatment must be continued longer than one year, the expediency of treatment reimbursement is under iterative consideration (Art. 11) (13).

Since the adoption of many new technologies for treatment of rare diseases is very expensive, Lithuanian Government takes a pragmatic approach to give the opportunity for orphan patients to get the treatment abroad. Such treatment and related consulting abroad can be organized for insured patients only when all available methods of diagnosis and treatment in Lithuania were exhausted and when there is a possibility to apply new supplementary methods of treatment and good results of them are forecasted (12).

The procedure case-by-case intended by such secondary legislation in some aspects could unfoundedly restrict the access of orphan patients to effective health care services and be in deviancy with the practice of the Court of Justice of the European Communities in the area of free circulation of medical services and goods (14).

Problem of definition

Comparing the definitions of "rare disease or condition" in the EU and Lithuanian legal documents discrepancy can be noted. The definition in the Decree (13) of the State Patient Fund Directorate at the Ministry of Health significantly differs from EU standard. "Very rare disease or condition" is defined as "discrete, individual/specific case of disease or condition, which occurs per year and for which there are no other ways of treatment reimbursement" (Art. 3) (13). Whereas the concept of "rare disease or condition" in the Regulation 141/2000 is closely interconnected with that of orphan medicinal products. The Regulation emphasizes the epidemiological aspect of the concept and defines it as "life-threatening, seriously debilitating, or serious and chronic condition, affecting no more than five in 10 thousand persons in the Community and there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question" (Reg. 141/2000 Art. 3) (6).

As for Lithuanian legal definition, it is not clear what does "individual/specific case" mean and to what extent the expression "discrete" includes the aspect of prevalence of the disease.

Looking from the legal point of view, such definition can be assessed as ambiguous, because the criteria that define the concept of a rare disease or condition are vague. The Committee, having the right to make a decision, is free to interpret this definition broadly; therefore, the access of orphan patients to effective health care services can be unfoundedly restricted. Such fears have reasonable grounds, because the budget assigned for reimbursement of orphan medicinal products is limited and certainly insufficient (6.5 million Litas in 2006). Consequently, in Lithuania, the situation of the patients suffering from rare diseases or conditions in terms of protection of patient rights is legally vulnerable.

Diagnostics of rare diseases

There is a general agreement within the scientific community that about 10% of the diseases suffered by human beings are rare disorders. It is estimated that between 5000 and 8000 distinct rare diseases exist today, affecting between 6% and 8% of the population in total – in other words, between 27 million and 36 million people in the 27 EU Member States (14). Majority of rare diseases (80%) have identified genetic origins (15, 16). Other rare diseases are the result of infections (bacterial or viral) and allergies or are due to degenerative and proliferative causes (15).

There are no official statistics or estimates on the overall number of people suffering from rare diseases in Lithuania. Theoretically, in accordance with worldwide rates, this number could reach approximately 240 000 persons on the average in Lithuania. Certainly, this extrapolated calculation (6–8% from 3.4×10^6 population of the Republic of Lithuania) is artificial as it does not take into account any genetic, cultural, environmental, social, racial, or other peculiarities for which statistics of rare diseases must refer to. Therefore, it may only give a general indication of rare diseases (including those of not genetic in origin) in Lithuania.

At present, the Center for Medical Genetics (CMG) at Santariškių Clinics of Vilnius University Hospital is the main authorized institution with activities focused on the diagnostics of congenital anomalies (inherited diseases and congenital malformations) in Lithuania. The main functions of the CMG are as follows: genetic counseling, prenatal diagnosis, nationwide newborn screening for inherited metabolic dis-

orders (17, 18). Currently newborns are screened for phenylketonuria and congenital hypothyroidism starting from 1975 and 1993, respectively. According to the CMG statistics (17), more than 99% (99.2 % in 2004; 99.6% in 2005) of all newborns have been screened. But there are known some preceding cases (19), when congenital hypothyroidism was failed to diagnose, and the patients did not receive the early replacement hormonal therapy.

Lithuanian Registry of Congenital Anomalies (LIRECA) is being carried out in the CMG from 1992. Any medical doctor who has diagnosed congenital anomaly/anomalies at birth must notify it/them to the Registry, but this obligation is not legally determined. Around 500–600 cases of congenital anomalies are being registered annually in Lithuania (17).

The Clinics of Kaunas University of Medicine are also engaged in genetic services, training, and research field of human and medical genetics, although on a smaller scale. Some genetic services are provided in Šiauliai Regional Hospital and Panevėžys Regional Hospital (18).

Usually, patients are referred to genetic counseling by outpatient clinics in e.g. pediatrics, gynecology, and neurology or by hospitals. However, links with primary care and with public care are not satisfactory because of general "insufficiency" of the health service as well as very poor knowledge and understanding of medical genetics amongst primary health care practitioners. Lithuanian jurisprudence already had several occasions to pronounce on the duties and professional requirements of physicians. An instructive example in the area of rare diseases is a case (20) where the girl, born in 1997, was not diagnosed with Wilm's tumor (nephroblastoma) for three years by primary medical doctor. The Supreme Court of Lithuania on the decision in 2002 stated that a failure to diagnose a disease timely, even without clinical and laboratory tests, because symptoms were obvious (asymmetric body, abnormal stomach, painful formation in the left side of the stomach, etc.), constituted medical negligence.

An inefficient system of diagnostics and treatment could lead to violation of the right to effective treatment, so the diagnostics of newborn rare diseases, when allowed by medicine achievements, should be accessible, timely, and effective. Patients should be followed up and treated by specialized medical professionals. The whole medical care of the patients with rare diseases is often multidisciplinary, so special attention should be turned to the some reorganization of genetic services. Firstly links with other specialists (secondary, tertiary) as well as links with primary care should be developed.

Clinical trials on orphan investigational medicinal products

An important though eventual means to ensure the access of orphan patients to effective treatment are participation in clinical trials (CTs). As CTs for medicinal products in orphan populations are subject to the same requirements for ethical conduct, efficacy, and safety as other medicinal products, investigators performing trials of orphan medicinal products are faced with several challenges that are not usually encountered in CTs of larger populations (21). In the case of rare diseases, clinical scientists are likely to find that a trial of sufficient size to provide a definitive answer is virtually impossible because of the difficulty of recruiting sufficient patients. A study of sufficient size would need to recruit from very large areas over long periods. Such studies are expensive and difficult to organize. Therefore, CTs of orphan medicinal products are needed to be conducted at multiple sites (9, 22).

After implementation of the EU Regulations in national legislation, in the Baltic States the number of clinical trials aimed at orphan medical products remains low. Between May 2004 and June 2007, there were approved only 4 CTs on orphan investigational medicinal products (IMP) in Lithuania (total number of CTs is 301 in Lithuania). The situation in Estonia and Latvia is even worse: only one CT on orphan IMP in Estonia and no CTs on orphan IMP in Latvia at all.

The presumable reasons of such a situation are limited number of patients, not coordinated and harmonized national and international networks between centers and clinics, limited knowledge of experts, major lack of information about the ongoing clinical research, legal boundaries to organize CTs with children or noncompetent people (23), lack of active advocate groups for patients suffering from rare diseases as well, etc. (5).

Nowadays there are only few specific organizations for orphan patients in Lithuania (Lithuanian Cystic Fibrosis Association; the Society for Phenylketonuria; the society for parents with children, suffering from onco-hematologic diseases; the society for Crohn's disease patients and some others). For many of rare diseases they do not exist at all. The experience of some EU Member States (Denmark, Italy, France, Poland, Spain, The Netherlands, United Kingdom), (5, 24) where rare disease patient organizations often actively support scientific and medical research into

their rare disease, for Lithuanian orphan patients could serve as an example. This can take the form of funding a research project; participating in clinical trials; or undertaking advocacy and awareness campaigns to encourage scientists, universities and medical schools, governments or pharmaceutical companies to devote resources to research into the disease and develop therapies for it (24). Active patient organizations should be established in Lithuania to help those in need. They should unite into groups and collaborate with other patient groups abroad. Medical care for patients affected with rare diseases as well as their families needs to be organized in the form of national reference centers and in cooperation with international services. Number of them should be no less than five and they should be specialized. Their activities should involve the provision of specialized aid and treatment for orphan patients; public communication about the problems of orphan patients; creation of national database for rare diseases. Italian experience when patients registered at orphan centers get reimbursement for their treatment and other services related to it could serve as an example.

In order to increase the number of CTs aimed at orphan IMP, all efforts must be taken. For example, the orphan medicinal products authorized by the centralized procedure should be further investigated in surveillance studies, proceeded in all EU Member States, and supported by the EU. These studies should contribute to collecting as much information as possible on the safety and efficacy of these products.

Conclusions

These results indicate that legal framework for rare diseases and their treatment in Lithuania should be further worked out. This could imply adoption of a special law and/or related secondary legislation. The following legal acts are necessary: to foster inter-institutional cooperation, to set up a national network for rare diseases, to establish national centers for rare diseases. There is a need for awareness raising among Lithuanian Government, health care specialists, patients organizations to improve practical implementation of EU legislation and progressive experience of EU countries in this field.

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Retomis ligomis sergančių pacientų situacijos Lietuvoje teisinis vertinimas

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Raktažodžiai: teisinis reguliavimas, pacientų teisės, retos ligos, retieji vaistai.

Santrauka. Lietuvai įstojus į Europos Sąjungą, nacionalinės teisinės sistemos dalimi tapo reglamentas 141/2000 „Dėl retųjų vaistų“ bei jį papildantis reglamentas 847/2000. Šie teisės aktai – tai retųjų vaistų ir ligų politikos, įgyvendinamos Bendrijoje, dalis. Valstybės-narės įpareigotos imtis veiksmų gilinant žinias apie retas ligas, jas diagnozuojant bei gydant.

Straipsnio tikslas – panagrinėti teisinius aspektus, susijusius su retų ligų gydymo reglamentavimu, išryškinti aktualiausias problemas, kurių atsiranda retomis ligomis sergantiems pacientams Lietuvoje, pasiūlyti galimus jų sprendimo variantus. Tai atliekama lyginant Europos Sąjungos ir Lietuvos teisės aktus dėl retųjų vaistų, taip pat atsižvelgiant į Europos šalių patirtį, kuri aiškėja analizuojant valstybių narių ataskaitas dėl veiksmų pastaraisiais metais šioje srityje.

Lietuvoje retomis ligomis sergančių pacientų teisių įgyvendinimą galima vertinti kaip nepakankamai teisiškai apibrėžtą. Tiek teisinės, tiek praktinės nacionalinės iniciatyvos ir veiksmai retų ligų ir vaistų srityje taip pat nepakankami. Tam tikri teisiniai aktai ir procedūros traktuotini kaip nepagrįstai ribojantys vaistų prieinamumą bei pacientų teisę į kokybišką sveikatos priežiūrą.

Lietuvoje turėtų būti tobulinama retų ligų gydymą reglamentuojanti teisinė bazė, teisiškai įtvirtintas įvairių sričių sveikatos priežiūros specialistų bendradarbiavimas (teisės ir pareigos) retų ligų diagnostikos, gydymo ir konsultavimo srityse, skatinamas aktyvių pacientų organizacijų bei nacionalinių konsultacinių centrų retomis

ligomis sergantiems pacientams kūrimas, retųjų vaistų klinikiniai tyrimai, informacijos teikimas valstybės valdymo institucijoms, medikams ir visuomenei, rūpestis dėl problemų, su kuriomis susiduria retomis ligomis sergantys pacientai.

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