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The Italian approach to rare diseases and the action of the Italian National Centre for Rare Diseases

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Abstract

The European Commission, recognizing that a number of healthcare and knowledge issues are common to all rare diseases in spite of the wide variety of their clinical manifestation, has recently initiated the promotion of national plans and comprehensive strategies for improving the provision of care to rare disease patients.
In Italy, for some time, a number of coordinated initiatives have been undertaken at National and Regional level in order to provide quality care to rare disease patients. Some of these initiatives anticipate the recommendations at the European Union level.
A key legal instrument has been the Ministerial Decree 279/2001 which established, with the collaboration of the Regions, the national network for the surveillance, diagnosis, treatment and cost exemption for rare diseases. Other regulations facilitate access to drugs and to assistance for the disabilities associated with rare diseases. More recently specific initiatives have been adopted to foster research on rare diseases and the involvement of patients in decision making regarding rare diseases.
Another key step in the development of an effective strategy to tackle rare diseases in Italy, has been the establishment of the National Centre for Rare Diseases. The Centre is currently developing a wide variety of initiatives: some contribute to the full implementation of the national legislative provisions and to the coordination of activities among the Regions; others aim to develop autonomous initiatives within its mission of research, provision of technical expertise and documentation as well as information on rare diseases.

Key words: rare diseases, surveillance, genetic tests, quality assurance, coding, social inclusion, patients' empowerment

Introduction

The specificities of rare diseases

According to the EU definition, rare diseases (RDs) are characterised by a prevalence of less than 5 / 10000 in the general population. Yet, they make up a considerable public health burden due to their high number. The European Commission [1] reports that the number of existing rare diseases is estimated to be between 5000 and 8000, affecting a total of 6-8% of the population. RDs are distinct by specific clinical and pathogenetic characteristics, but their social and health impact shows a number of common features. Onset occurs, in about half of them at birth or during infancy, while the rest appear during adulthood. They are associated often with premature mortality and long lasting and severe disability. Another common feature is the challenge they pose to the health system for the provision of timely and appropriate care.

Among the most common RDs are: Sclerodermia, Charcot-Marie-Tooth disease, Marfan syndrome, Retinitis Pigmentosa, Neurofibromatosis, Turner syndrome, Hemophilias, Sickle cell disease, Cystic fibrosis and Duchenne Muscular Dystrophy. Some other very rare diseases are known to the general public despite their rarity, such as Huntington disease and Creutzfeld Jacob disease. The most frequent diagnosis notifications to the Italian National Register for Rare Diseases refer to congenital coagulation defects, connective tissue disorders, hereditary anaemias, ALS, neurofibromatosis and congenital iron metabolism disorders. At present, however, no sound data on the occurrence of rare diseases are available. Orphanet [2], a European portal of information on rare diseases, which currently provides the most comprehensive inventory of rare diseases, reports that only 105 are estimated to have a prevalence ranging from 5 to 1 in 10.000 and 233 RD to have a prevalence ranging between 1 in 10.000 and 1 in 100.000. Another 1.000 RD

have probably a prevalence of around 1 per million. Such low prevalence figures imply that, for some diseases, there are as low as a few tens of patients in the European Union. For others, it is possible that a general practitioner may see only one case in his/her whole career. The existence of specialized centres may even be unknown to some professionals. Therefore, their low occurrence makes them little known and the related expertise scant, resulting in delayed diagnosis, difficulties in assessing the proper management of patients and in emotional impact on the patient and his/her family.

The limited market represented by the single pathologies makes the development of new drugs and treatments unattractive to the pharmaceutical industry. As a consequence, drugs for RDs are available for only a few diseases: to date, 56 orphan medicinal products are on the market in the European Union; moreover, they are usually expensive, making them inaccessible for the large majority of families; finally, their efficacy and safety can be seldom be thoroughly assessed. These conditions have led many countries in the world to the development of specific regulatory schemes to be applied to drugs designated as "orphan medicinal products" and to facilitate access for disease patients to orphan and other drugs. In spite of these efforts, a survey, on the access to orphan drugs in Europe (including prices, reasons for unavailability, level of reimbursement, population of patients treated etc.), showed that access differs between countries with access, in general, being considerably delayed [3].

The EU Recommendation

The European Commission in its Communication of 11 November 2008 to the European Parliament and Council on "Rare diseases: Europe's challenges" analysed comprehensively the issues associated with the provision of care to RD patients [4]. Following this Communication, the Council of the Health Ministers of the EU recognized the need for a Community action in the area of RDs [1] and issued a number of recommendations for actions to be considered by the Member States. They include the integration of relevant national actions in the field of rare diseases into comprehensive plans or strategies, to be issued by 2013, in order to improve the coordination and coherence of national, regional and local initiatives addressing rare diseases and cooperation between research centres; the development of an appropriate classification and coding, in order to improve the visibility of RDs and their recognition in the national health system; the adoption of a common classification in all EU Member States, the identification of qualified Centres of expertise for diagnosis and care of RD and their participation in European Reference Networks in order to facilitate cooperation among Member States and the movement of experts to improve the access of RD patients to high quality care; establishment of an inventory for projects and resources dedicated to RD research, identify needs and priorities and devise financing schemes to support research and facilitate its coordination at national, Community and international levels; gathering of expertise at Community level in order to facilitate sharing of best practices for diagnosis and care, adequate education and training for health professionals, guidelines on diagnostic tests and population screening, as well as sharing national assessment reports on orphan drug added value. The Council Document also recommended the involvement of patient representatives in the development of policies and in other activities aiming at patient empowerment, such as awareness-raising, capacity-building and training, exchange of information and best practices and support of very isolated patients.

These EU Recommendations reflect some of the achievements of the ongoing action and commitment of the European Commission. Indeed, to raise the attention and improve the information on rare diseases, the European Commission has, since 1997, mainly been financing projects that aim to collect information on centres of expertise, establishing or consolidating European registries and networks of experts on rare diseases and, finally, to develop common guidelines for newborn screening. The European Commission is also co-funding a project (EUROPLAN), that aims to promote the implementation of the EU Council Recommendations on Rare Diseases in the EU Member States.

While France adopted a national plan on rare diseases in 2005, many EU Member States have been launching a number of initiatives concurrently or subsequently to the EU Council Recommendation. National plans or strategies of different complexity and with different aims have been adopted in Bulgaria, Greece, Portugal, Romania and Spain. Other EU Member States are currently preparing their plans. An inventory of the initiatives undertaken in the EU Member States is being produced by EUROPLAN

(www.europlanproject.eu) in conjunction with Orphanet.

The Italian strategy

Italy has adopted a number of measures for the care of rare diseases. The three year National Health Plans, which are intended as directions for actions to be followed in the entire country, have been indicating since 2001 that rare diseases are among the priorities for the health care system.

Moreover, in 2001, the Ministry of Health issued a Decree (DM 279/2001) [5] establishing the national network for rare diseases and cost exemptions for related health service provisions. The main aim of this Decree was to set rules for cost exemptions for services included in the Essential Care Levels (LEA: Livelli Essenziali di Assistenza) and to identify specific protective measures for rare disease patients. To address this aim, the Decree established a national network of Centres for the prevention, surveillance, diagnosis and care of rare diseases. With reference to surveillance, it has included the provision for the establishment of a national registry of rare diseases, connected to multiregional registries and, through them, the ability to receive epidemiological, clinical and other data from qualified Centres designated by the Regional authorities. The Decree also set a list of rare diseases, including 284 single and 47 groups of rare diseases, to facilitate referral of suspected patients to the appropriate diagnostic Centre, to waive costs for diagnostic tests and to speed up assistance of patients with confirmed diagnoses. The list of rare diseases can be updated based on the progression of scientific and technological knowledge, the epidemiology of diseases and diagnostic and therapeutic pathways. To date an additional 109 conditions have been identified and are waiting for official recognition by the health authorities. Another important provision set out by the Italian Council of Ministers (DPCM of 9 July 1999) [6] was the mandatory performance of the newborn screening tests for three rare conditions: phenylketonuria, congenital hypothyroidism and cystic fibrosis. Indeed, the early identification of patients affected by these diseases before the clinical onset of symptoms, could allow for treatments that prevent the evolution of these diseases into severe disabilities.

The Italian health care system has delegated the responsibility for the provision of health services to the regional health authorities. Based on a decision from the State-Regions Conference, a standing inter-regional technical group, made of Regional Representatives, the Ministry of Health and the National Institute of Health) was established in 2002.Their mandate is to ensure the coordination and monitoring of health care activities regarding RDs, with the aim of optimising the operation of the Regional networks and safeguarding the principle of equity in healthcare for all citizens. Each Region identified its own reference Centres for rare diseases to be part of the National Network for Rare Diseases. The Regional Centres were identified among those possessing documented experience in diagnostic or specific therapeutic activities and endowed with adequate structures and complementary services (emergency services and services for biochemical and genetic-molecular diagnosis). Moreover, by virtue of their competences, four Regions (Marche, Piemonte, Toscana and Valle d'Aosta) adopted a list of rare diseases that was more extensive than the one established at the national level, and two Regions (Toscana and Veneto) have recently decided to undertake population wide newborn screening that has been expanded to cover more than 20 rare diseases. Regional activities that address rare diseases have received 30 Million Euro in financial support based on the Financial Law 2007.

The pharmaceutical industry has limited interest in the development of drugs intended for the treatment of RD patients, due to the limited market and profit expected. EMEA has developed an evaluation process, shared by all EU Member States, for the designation of drugs as orphan drugs, thus ensuring their availability by means of incentives for their production. However, there is still the possibility, depending on the requests for registration and on the national registration procedures, that some orphan drugs are at least temporarily available in a Country and not in another. Moreover, some drugs used for other diseases, may be presumed to be effective for a rare disease, which is not indicated in the label. A number of general provisions have been issued in Italy, which are of particular advantage for RD patients.The law 648/96 [7] allows, on the costs of the National Health Service, the use of drugs marketed abroad; the use of drugs not authorized but subject to clinical trial; and the off-label use of drugs. Such uses need to be authorized by a Scientific Committee and should be reported in a list which is periodically updated.The off-label use of a drug, on the costs of the National Health Service, can be also decided by a doctor, as envisaged by art. 3, paragraph 2 of DL 23/1998 [8], provided that it will be decided patient-by-patient, will not be continuous, is supported by documented evidence and/or results published

on internationally renowned journals and no alternative treatments are possible. Finally, a drug, which is not authorized but is subject to phase II or III clinical trials for the same therapeutic indication, and which appears to result with a likely favourable evaluation of efficacy and safety, can be prescribed to one patients or groups of patients on the costs of the producer [9].

Patients suffering from disabilities associated with RDs are eligible for assistance, including not only compensation for reduced working ability, but also integration at work, on the basis of the current general regulations for civil inability. In particular, Law 118/71 [10] refers to congenital and acquired inabilities, including those of a progressive nature, which result in a permanent reduction in the working ability as well as, for those patients younger than 18, it also covers permanent difficulties related to performing tasks and activities typical of their age. Following this, a legislative decree [11] extended the definitions set by Law 118/71 to include the permanent functional impairments resulting from physical and/or psychical and sensory illnesses. Moreover the definition of inability that applied to patients younger than 18, was extended to cover those older than 65.

The Ministry of Health, the National Institute for Health and the Italian Drug Agency promote research programmes dedicated to Orphan Drugs. The last call for projects on Rare Diseases, published by the Ministry of Labour, Health and Social Policies, received eight million Euros in funding. Moreover, the Ministry of Labour, Health and Social Policies, the National Institute for Health and the Ministry of Education, University and Research financially support the participation of Italy in the ERA-net scheme for rare diseases (e-RARE). Voluntary donations for a number of research institutions are also promoted by means of tax deductions and facilitated by yearly fiscal declarations.

The decision-making process regarding measures for rare diseases recognizes patients as essential actors of the decision. Indeed, a "Consulta", made of a number of patients' associations has been officially established by the Ministry of Labour, Health and Social Policies in 2008. The Consulta is convened each third month to discuss legal documents, issues related to care and treatment and research for RDs. The patients' opinion is taken into account in decisions at national levels, although it is not binding.

Since 2000, the "Rare Diseases" Unit at the National Institute for Health (Istituto Superiore di Sanità - ISS) has been actively developing a wide array of national and international initiatives on rare diseases, some of which have contributed to the implementation of the Italian Network of Rare Diseases3. As a result of the strategic approach, developed over more than ten years, to tackle the public health challenges associated with RDs, this Unit has been the initial nucleus of the Italian National Centre for Rare Diseases (CNMR, www.iss.it/cnmr), which was formally established at the ISS in 2008, with the mission of research, provision of technical expertise and documentation on rare diseases and orphan drugs, aimed at prevention, treatment and surveillance. The Centre hosts a wide range of scientific and technical expertise (genetics, molecular biology, epidemiology, public health, psychology, sociology etc.) and participates in a network of national and international collaborative activities, which allow for the development of a multidisciplinary integrated approach to rare disease issues. CNMR regularly provides expert advice to the Italian National Health Service, to the Ministry of Welfare and to the Higher Health Council and collaborates with the Regions, which are responsible for the provision of health services in the Italian devolved health system. Expert advice on RDs is also provided at EU and international level with its ad hoc participation in scientific committee meetings of the European Food Safety Authority; in the European Commission Task Force on Rare Diseases (DG SANCO) and the Research Advisory Committee (DG Research), as well as in WHO and OECD Committees.

The current activities of CNMR have been developed to address the following main RD challenges:

Research on RDs

CNMR plays an important role in the coordination and promotion of national scientific and public health research, and participates in the Advisory Committee for European Research. In the framework of an agreement with US NIH, CNMR cares the implementation of a national programme of scientific research projects on RDs. CNMR carries out scientific research projects on the pathogenesis of selected RDs using advanced technologies (e.g.: bioinformatic methodologies, micro-RNA platform and CGH array). Moreover, CNMR carries out public health research on matters of relevance to its mission (e.g., epidemiology, service accessibility, identification of patients' needs); coordinates the EU EUROPLAN project, aiming at facilitating the implementation of the EU Recommendation on RDs; is partner of E-RARE, an ERA-net project for

the improvement of RD research infrastructures; and of TEDDY, an EU-funded network of excellence, which aims at improving the availability of safe and effective paediatric drugs.

Quality of RD diagnostic tests and patient management

CNMR participated in the OECD Panel of experts for the preparation of Guidelines for quality assurance in molecular genetics tests and in the EU-funded project "Multi-National External Quality Assay (EQA) programmes in Clinical Molecular Diagnostics". CNMR is member of the European Molecular Genetics Quality Network and participates in the EU-funded EuroGentest excellence network, aiming at the standardisation and harmonisation of quality of genetic testing in EU Member States. CNMR coordinates the National External Quality Assessment schemes, for a number of molecular genetic and cytogenetic RD diagnostic tests carried out in Italian public laboratories. CNMR is implementing a programme of guidelines for the management of rare disease patients; up to now several guidelines have been elaborated for the integrated multidisciplinary approach to the management of several RDs and syndromes. Moreover, CNMR monitors the publication, collects and makes available in its website guidelines prepared by national and international organizations.

Primary prevention

CNMR coordinates the Italian Network for the promotion of folic acid use in the primary prevention of congenital anomalies. The network is composed of more than 200 public and private organisations, including local health authorities, patients associations, scientific societies, research institutes and communication experts. It delivered a "Recommendation for the peri-conceptional use of folic acid" and is currently working towards the broad implementation of this recommendation. Moreover, CNMR is member of the ESCO group on "Analysis of risks and benefits of fortification of food with folic acid" at EFSA.

Epidemiological information

In collaboration with the regional registries, CNMR runs the National Register of Rare Diseases, which collects epidemiological information that assists in determining the dimensions of the issue and potential risk factors, as well as supports clinical research and the definition of diagnostic criteria. Currently this register contains more than 66000 records received from collaborating centres located in all other regions.

Orphan drugs

CNMR has established the National Register of Orphan Drugs to collect, for a limited time period after their initial marketing, data for the assessment of the appropriateness and safety of use of selected drugs newly authorised for the treatment of rare disease. From 2000 to 2009, the director of the CNMR has been the Italian member of the EMEA Committee of Orphan Medicinal Products (COMP).

Coding of rare diseases

CNMR coordinates a national committee for the improvement of the RD coding process and contributes to the classification and coding of RDs for the preparation of WHO ICD-11, within the EU Task Force on Rare Diseases, an advisory committee which operates by the EU DG Health and Consumers.

Continuing education and training for health professionals; patients' and families' empowerment

CNMR is developing a programme of continuing education in rare disease patient identification, referral and management addressed to GPs and other health professionals. CNMR has been carrying out, in collaboration with the Italian National Council of RD Patients' Associations, a number of courses, addressed to Patients' Associations, aiming at empowering RD patients, as well as their families, in the daily management of their disease.

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Information and communication on rare diseases

CNMR holds a portal on RDs (www.iss.it/cnmr) which provides information of interest to RD patients and includes a user friendly tool for searching disease-specific information. The Free Toll Telephone Number, while complementing the information offered by the web site, ensures a more direct psychological counseling of the

patients and provides expert answers to specific questions and needs. A CNMR Newsletter on RDs and Orphan Drugs, providing information on on-going research and public health activities on RD, is regularly published by Istituto Superiore di Sanità.

Narrative-based medicine

CNMR launched, in collaboration with a number of patients' associations, the project "Rare diseases and narrative-based medicine". This project aims at reducing social exclusion of RD patients and at promoting their participation in society. To facilitate patients in telling their own personal experience of the disease and to bring their stories to light so that they can be shared with the rest of society, raising awareness and reducing the barrier towards diversity and the unknown, a public contest of fine arts and literary works was organized for the first time in 2009. About 300 fine arts and literary works have been submitted to this competition, named Il Volo di Pegaso (The Flight of Pegasus). The best pieces were selected by a jury made up of literary and art critics and were awarded a prize during a public ceremony held on the European Rare Disease Day, which gained wide resonance and appreciation.

Conclusions

The EU Council Recommendations in the field of rare diseases are expected to result in a number of initiatives, which will extend and improve, in the next years, the provision of healthcare services in the European Countries in the field of rare diseases. Besides the actions which will be developed independently by the EU Member States, the EUROPLAN project will convene in 2010, in a number of EU Countries, national conferences, where local stakeholders and the competent health authorities will start a debate on the local implementation of national strategies for rare diseases. In Italy, the effects of the EU Council Recommendations will combine with the action of the recently established National Centre for Rare Diseases, which is working to facilitate and improve the implementation of a number of initiatives in favour of rare diseases. The regular functioning and complete population coverage of the National Registry for Rare Diseases, which is being achieved as a coordinated effort of the regional and national authorities and CNMR, will represent a formidable tool to improve the quality of healthcare and to build expertise and knowledge on rare diseases.

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