REVIEW

Piedmont and Aosta Valley inter-regional network in the context of the Italian National Network for rare diseases

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Introduction

In Europe rare diseases (RDs) are defined as "*diseases with a prevalence in the European Union (EU) population of less than 5 per 10,000*". This definition includes a large group of more than 6,000 diseases, 90% of which are genetically determined and which potentially involve all organs[1]. RDs are therefore a very heterogeneous group as far as both clinical and epidemiological aspects are concerned.

There are in fact RDs with less severe clinical manifestations and others with important ones which can compromise the quality of life and the life expectancy. Furthermore, some RDs have a prevalence approaching to the 5 per 10,000 limit and therefore affect a significant number of patients. Indeed, from the June 2005 to the December 2013 the Piedmont and Aosta Valley interregional register for RDs collected 21,062, with an estimated overall prevalence of RD of 45 patients on 10,000 inhabitants. Moreover half of the patients registered are affected by less than 20 diseases or groups of diseases (Table I) that represent the most important burden of care for the regional healthcare systems. On the other hand there are several with a much lower prevalence affecting a very small number of patients[2].

These latter often lack of timely and correct diagnosis and adequate treatment. Moreover, the world-wide orphan drug policies are associated with unacceptably high costs of newly developed drugs and inaccessibility of previously available drugs which become unavailable over time because of limited production by pharmaceutical industries[3].

Finally, despite the low prevalence of each disorder, the number of rare disease is fairly high. The European Commission reports that RDs affect a total of 6-8% of the population.

Due to all these problems, and to the fact that RDs are often chronic and invalidating or cause early mortality, they represent a significant public health matter of concern in many countries.

The Italian regulatory framework on RD

In Europe the problem of RDs was addressed for the first time by The Program of Community Action on rare diseases 1999-2003[4].

Italy was one of the first European countries to develop specific regulations regarding RDs[5]. Since 1998, the three year National Health Plans has been issued, intended as national-wide instructions. This document indicated RD as a priority for National Health Service (NHS). Moreover, in 2001, the Ministry of Health

Table I - Distribution of diseases covering 50% of reported diseases in the Piedmont and Aosta Valley Rare Diseases Registry.

Rare disease or group	n. of patients	%	Cumulative %
Hereditary coagulation disorders	1,245	5.9%	5.9%
Lateral amyotrophic sclerosis	997	4.7%	10.6%
Hereditary anaemias	981	4.7%	15.3%
Progressive systemic sclerosis	888	4.2%	19.5%
Congenital metabolic iron disorders	745	3.5%	23.1%
Neurofibromatosis	607	2.9%	25.9%
Undifferentiated connective tissue disease	548	2.6%	28.5%
Sarcoidosis	487	2.3%	30.9%
Chronic idiopathic thrombocytopenic purpura	474	2.3%	33.1%
Antiphospolipids syndrome	451	2.1%	35.2%
Keratoconus	419	2.0%	37.2%
Idiopathic pulmonary fibrosis	399	1.9%	39.1%
Genetic arrhytmias	359	1.7%	40.8%
Down syndrome	358	1.7%	42.5%
Disorders of aminoacids metabolism and transport	356	1.7%	44.2%
Arnold-Chiari syndrome	337	1.6%	45.8%
Muscular dystrophies	332	1.6%	47.4%
Lichen sclerosus et atrophicus	289	1.4%	48.8%
Bullous pemhigoid	271	1.3%	50.1%

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comprehensively addressed the issue of RDs with a specific Decree (DM 279/2001)[6].

DM 279/2001 established the national network for RDs and cost exemptions for related health service provisions for a consistent cohort of RDs[5]. DM 279/2001 also established a National Registry of RDs to be kept at the National Institute of Health[7]. A few months after the publication of DM 279/2001, a Constitutional Law (Constitutional Law 3/2001) reformed Title V of the Italian Constitution. Several decisions on health, including RDs, were consequently delegated to the regional administrations. As a result the development of networks for RDs was quite different among the various Italian Regions.

Prior to DM 279/2001, other national laws had dealt with specific RDs, such as cystic fibrosis and hereditary haemorrhagic diseases. For instance, as addressed in other papers in this issue, a network of reference centres for haemophilia and related disorders was already operating before 2001.

The inclusion of these previously existing network for specific RDs was one of the problem faced by regional administrations in implementing DM 279/2001.

The regional RD networks: examples from the current experiences

The network of RDs was implemented following different organisation systems in various Italian regions.

In some of the smaller regions with a small population, such as Marche region, one or two reference centres paediatric and adult patients were established[8].

In other regions, such as Veneto, reference centres for homogeneous nosological groups of diseases were set up. Moreover, these regions have created a network for local care in order to provide a day to day patients take in charge[9].

A similar model was applied by the Tuscany region where a diagnostic network made up of reference centres and a care network interact with each other to manage the patient's healthcare needs[10].

Contrarily, the Lombardy Region applied a model based on establishing reference centres on which insist all the aspects of the diagnosis and care of the patient[11].

A final model is the "hub and spoke model" which is implemented, for example, by Emilia Romagna. This model bases on concentrating the more complex cases in a limited number of centres (hubs). The clinical activity of the hub is highly integrated through functional connections with that of the peripheral health centres (spokes)[12].

All the above models are based on establishing reference centres which are entrusted for the diagnosis of the disease and to supply the appropriate therapeutic prescription. In most cases the reference centres were established considering the number of treated patients and the scientific relevance of each centre. In some regions, such as in Lombardy, the reference centres are subject to periodic re-evaluation by a local coordinating Centre which evaluate all the above mentioned parameters.

Some regions have made inter-regional agreements. Therefore there are two formally recognized inter-regional areas. The first one is made up of Piedmont and Aosta Valley. The second includes Veneto, the Autonomous Provinces of Trento and Bolzano, Friuli-Venezia Giulia, Emilia-Romagna, Liguria, Puglia and Campania[13,14]. The regions involved in the two inter-regional networks share the same policy for the accreditation of reference centres, the information system for the management of the Registry of RDs, treatment protocols, and standards of care.

Finally, in 2006, all the Italian Regions and Autonomous Provinces joined in an inter-regional network for RDs with the purpose of a joined approach to common issues such as home administration of drugs for metabolic diseases and telemedicine.

The Piedmont and Aosta Valley network for RDs decentralised model

The Piedmont and Aosta Valley Inter-regional Network for RDs was developed in 2008. It is the result of the union between two previously separate systems, i.e., the Piedmont regional network for RDs, founded in 2004, and the system for RDs in the Aosta Valley region[14,15]. It is a decentralised organisational model based on the active involvement of all the professionals operating in the public health system of the two regions.

The Piedmont Network for RDs was created to guarantee equal opportunities of assistance throughout the Region, develop diagnostic and treatment protocols to be shared among physicians, provide information on regional health organization and legislation to care-givers and patients' associations. It has also be created to collect data for epidemiological studies through the Regional Registry, allowing to identify both critical problems (including delays in diagnosis and care) and areas of possible investment of resources.

The Inter-Regional network for RDs was designed to develop a model of healthcare assistance that would guarantee the quality of diagnosis (including genetic analysis) in centres with proven expertise. More importantly, it aims to offer appropriate healthcare to patients as close as possible to their place of living. Thus, the Piedmont and Aosta Valley model of decentralised network for RDs is unique among the Italian experiences. Unlike most networks in other Italian regions, the Piedmont and Aosta Valley network involves all the healthcare facilities within the regions, thus giving all the specialists the opportunity to be

involved in treating patients with RDs.

A network as widespread as that of Piedmont and Aosta Valley requires a Coordinating Centre and a monitoring system to evaluate the appropriateness of diagnoses and therapy. The Coordinating Centre was established in 2004 and, since 2005, it has been supported by a regional technical board[15,16]. The coordination of clinical activities for RDs throughout the two regions is guaranteed by Working Groups for RDs operating in all heath institutions of the public regional systems that act in collaboration with the Coordinating Centre. The supply of drugs for treatment of patients suffering from RDs is ensured by a wide network of hospital pharmacies. These provide all the needed medicinal products including drugs not currently available nation-wide or still under investigation in selected cases, and off-label agents. In addition, they also produce galenic preparations which are essential for the treatment of specific RD. The network of collaboration for the productions of galenics among hospital pharmacies is, to date, unique in Italy[17].

Another peculiarity of the network of RDs in Piedmont and Aosta Valley is the presence of multidisciplinary working groups, called Consortia, dedicated to specific RDs or to RDs with similar therapeutic or diagnostic problems. They operate throughout the two Regions and are composed of volunteer clinicians, other health professionals, and patient's associations. Consortia main goal is the development of shared protocols and clinical pathways[18,19]. The Consortia deal with the most prevalent RDs, or with the ones that are characterised by specific issues such as the cost of treatment or the lack of reliable data regarding treatment effectiveness and efficacy.

Twenty two Consortia were active at the end of 2013. Fourteen disease-specific or disease group-specific clinical pathways have been implemented to date (Table II).

In addition to developing the clinical pathways, the Consortia also identify, if needed, Centres of Expertise. A Centre of Expertise must have proven diagnostic and therapeutic experience as well as availability of appropriate support structures and complementary services, such as laboratory and imaging facilities, emergency department availability, etc. The main aims of the centres of expertise are supporting the local health authorities in the care of patients, and providing specialised training to the health professionals. To date, Centres of Expertise have been established for amyotrophic lateral sclerosis, for syringomyelia, and Arnold-Chiari syndrome.

Lastly, an important activity of the *Consortia* is the production of clinical and epidemiological studies on RDs[19-24].

The Piedmont and Aosta Valley network for rare diseases is also involved in international collaborations, such as the network International Conference for Rare Diseases and Orphan Drugs, Europlan initiatives promoted by the National Institute of Health, by the European Community, and by Eurordis, and in the rare diseases coding promoted by World Health Organization and by Orphanet.

Table II - Multidisciplinary working groups (so-called Consortia) at December 31, 2013. In bold are indicated the implemented clinical pathways.

Adrenogenital Syndromes
Amyloidosis
Anti-phospholipid Syndrome
Arnold Chiari Syndrome, Syringomyelia
Autoimmune peripheral neuropathies
Autoimmune Polyendocrinopathies
Bladder Pain Syndrome
Congenital Osteodystrophy
Hereditary coagulation Disorders
Hereditary retinal dystrophy
Klinefelter Syndrome
Neurofibromatosis
Lysosomal Storage Diseases
Porphyrias
Prader-Willi Syndrome
Precocious Puberty
Primary Lymphedema
Primary Pulmonary Hypertension
Systemic Sclerosis
Transition from childhood to adulthood
Undifferentiated Connective Tissue Disease
Uveitis

Conclusion

The network of RDs in Piedmont and Aosta Valley is a unique experience in the Italian scenario. An analysis of 10 years of activity allows us to give a largely positive assessment. This widespread network has improved the clinicians' knowledge of the specific RD.

Moreover, the clinical activities of the Consortia and of the Network of Hospital Pharmacies allowed to provide appropriate cares to patients and to limit both the costs and the therapeutic healthcare mobility toward other regions.

Authorship contributions

Simone Baldovino and Elisa Menegatti participated equally to the first draft of the paper.

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