Uncovered needs in the management of inherited bleeding disorders in Italy

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Introduction

Haemophilia is an X-linked bleeding disorder[1] and is characterised by repeated bleeding, especially in joints. The current management of haemophilia is based on the replacement therapy with intravenous clotting factor and includes plasma-derived and recombinant factor concentrates[2]. The early treatment in pediatrics age has been recognised as an important determinant of better physical development[3], and several studies have demonstrated that primary prophylaxis has a positive and significant impact on the quality of life and the prevention of arthropathy in haemophiliac children[4,5]. Also, home treatment has shown to improve both life expectancy and quality of life of patients with haemophilia[6].

The global treatment of haemophilia, however, requires a multidisciplinary team including haematologists, physicians, surgeons, orthopaedics and other specialists in several medical areas[7]. This level of clinical assistance is or can be guaranteed only in some countries, and this influences the life expectancy of haemophiliacs[8].

To ensure a high quality of haemophilia care, an appropriate health organisation and economic resources are necessary.

The European Principles of Haemophilia Care (EPHC) were published in 2008[9]. These Principles detail the standard of haemophilia care that should be achieved for an appropriate global care of persons with haemophilia (PWH).

The aim of this review is to highlight uncovered needs of Italian haemophilia community, relative to the implementation of each of the EPHC.

A central haemophilia organisation supporting local groups

Patient and medical bodies, represented in Italy by the Italian Federation of Haemophilia Societies (FedEmo, www.fedemo.it) and the Italian Association of Haemophilia Centres (AICE), are national organisations that have addressed the problems of PWH since 1996. Because the Italian National Healthcare Service gives to the 21 Regions political, administrative and financial responsibility regarding the provision of health care, each Region may develop its peculiar healthcare organisational model[10]. In the majority of the largest Regions (i.e. Emilia-Romagna, Latium, Lombardy, Campania), the network of hospital care is most frequently organised following a "Hub and Spoke" model. For improving the organisation of hemophilia care and the access to services, in 2009 FedEmo asked the Health Commission of the Conference between the Italian State and Regions for the development of an accreditation system for Haemophilia Centres (HCs)[11]. Following this request, in 2010 the Ministry of Health funded a project aimed at developing a model of disease management to prevent haemophilia complications. Given this background, FedEmo, AICE, the Italian National Blood Center (NBC, www.centronazionalesangue.it), Italian Regional Health Authorities and Ministry of Health proposed an institutional accreditation scheme for HCs, that was approved by a formal State-Regions Agreement in March 2013[11,12] (hereafter referred as the March 2013 Agreement). This provides an organisational framework for Italian Regional Health Authorities to optimise and standardise haemophilia care on the basis of the latest scientific evidence and international recommendations[9,13].

National Haemophilia Patient Registries

In Italy, the epidemiological data on inherited bleeding disorders derive from the Italian National Registry for Rare Diseases (NRRDs), the National Registry of Congenital Coagulopathies (NRCC) and the Italian Registry of Haemophilia and Allied Disorders of the AICE[14].

NRRDs is a population-based and multi-diseases register established by law since 2001, that supports national planning of interventions for patients affected by

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rare diseases (RDs) and implements the epidemiological national surveillance of RDs.

NRCC was activated in 1999 by the AICE and the National Institute of Health (Istituto Superiore di Sanità, ISS, www.iss.it). The main objectives of the National registry of congenital bleeding disorders is to: i) estimate the prevalence of different congenital bleeding disorders, ii) evaluate therapy complications with particular attention to infection diseases (HIV, HCV, prioni), iii) monitor the appearance of inhibitor antibodies, iv) monitor the appropriateness of treatment[15].

In 2003, AICE also created a new pathology registry: the Italian Registry of Haemophilia and Allied Disorders (www.aiceonline.it). A subset of data is shared between the two registries. The main objective of this registry is to collect data on current clinical practice and provide data for clinical studies[16].

The registries differ in terms of organisation, purpose and data collection process. They provide epidemiological data on inherited bleeding disorders but at this stage do not fully support benchmarking activities of HC performance.

Comprehensive Care Centres (CCCs) and Haemophilia Treatment Centres (HCs)

The current management of haemophilia should improve the health and quality of life for PWH. This issue could be achieved with the following two actions.

Firstly, establishing a team of specialists in CCCs and HCs, providing a continuous comprehensive care based on three main goals: i) prevention of bleeding, ii) management of joint and muscle damage, iii) management of treatment complications (inhibitor antibodies and viral infections).

Secondly, offering an equal access to CCCs and HCs on all the national territory.

In Italy, the availability and quality of care vary widely within the country, so that 52% of patients must still travel long distances (101-500 km), 22% of those living in Southern regions and islands travel more than 500 km, and 40% of patients had to change living place to attend a HC with an optimal level of care[17].

Nowadays, there is a wide difference in the organisation and efficacy of the HCs in Italy. However, commitments endorsed by Regions within the March 2013 Agreement provide the ground for an improvement and standardisation of haemophilia care across the Country. So far, three Regions (Autonomous Province of Trent, Emilia-Romagna and Liguria) over 21 have accepted the March 2013 Agreement into their legislation. Uncertainty remains about the way HCs regional network should be funded.

Partnership in delivery of care

The 4th Principle of EPHC declares that the etablishment of an Haemophilia Co-ordination Group is desirable. This group should be represented by physicians, national haemophilia patient organisations and national health authorities. Unfortunately, so far an Italian national haemophilia Co-ordination Group has been missing but a local haemophilia Co-ordination Group is active in a few regions.

Some aspects related to the comprehensive care such as pharmacological treatment, organisation and access to specialist services have to be included in the national program.

Allocation of economical and structural resources is of primary importance and, to such aim, an effective partnership between different stakeholders has to be defined to draw up the priorities and define national clinical and organisational recommendations.

Safe and effective concentrates at optimum treatment levels

Actually, the treatment for haemophilia has reached a high degree of effectiveness and safety[2]. In 2011, even if with a wide variability across Regions, a standardised national consumption of factor VIII and factor IX respectively of 6.5 and 0.9 international units (I.U.) *per capita* has been achieved[18]. In Italy, guidelines for diagnosis and treatment of patients affected by coagulation disorders have been produced by AICE in the past years[19,20]. Very recently, a revised version has been approved and will be shortly published. This document carefully considers all the available products and the different mainstay of the treatment (home treatment, prophylaxis, ITI).

A scientific and economical debate on products type, such as recombinant *vs* plasma-derived, is ongoing[21-24] basing on the difference between the two classes of products and mainly on the costs.

As we believe that the quality of life of patients represents one of the more desirable outcome of care, we would recommend instead evaluating individual treatment taking into consideration pharmacokinetic response, efficacy, side effects, outcomes, patient's inhibitor history, preference and compliance[25,26].

Home treatment and delivery

Home treatment has shown to improve both life expectancy and quality of life of patients with haemophilia and other inherited coagulation disorders, with a reduction of musculoskeletal damage[6,7].

In Italy, home treatment is a common practice, but a specific regulation on self infusion has been adopted in only 60% of Italian Regions (Calabria, Campania, Emilia-Romagna, Latium, Liguria, Lombardy, Piedmont,

Apulia, Sardinia, Tuscany, Autonomous Province of Trent and Veneto).

Prophylactic (preventive) treatment

In Italy, prophylactic treatment is now available in all Regions without financial constrains and regular concentrate availability. The SPINART study (Trial to Evaluate the Effect of Secondary Prophylaxis with Recombinant FVIII Therapy in Severe Hemophilia Adult subjects compared to That of Episodic Treatment)[27] and the POTTER study (Prophylaxis vs On-demand Therapy Through Economic Report)[28] are eagerly awaited as they could lead to redefine the guidelines on treatment for haemophilia. We believe that the prophylactic treatment should be offered to all PWH -including adults- to maintain a high quality of life.

Specialist service and emergency care

With regard to the management of haemorrhagic emergencies, in 2011 only 36% of the Italian Regions had set up a specific protocol, 68% had emergency units with immediate availability and access to factor concentrates, only 58% of HCs had a physician expert in haemostasis available 24/24 h and 42% had 24 h access to a coagulation laboratory able to perform inhibitor detection and titration[29].

This picture represents a limitation of access to appropriate care, and therefore the Italian haemophilia community should develop specific plans with the related stakeholders. Indeed, in an emergency care setting accessibility to drugs, appropriateness and competence are critical issues and these are the areas needing to be improved, to avoid severe complications and inequity. In order to improve the awareness about this issue, FedEmo launched in 2011 an educational project called "Safe Factor" involving the key actors involved in emergency care like physicians of HCs, emergency departments, pharmacist, etc. We expect from this campaign and from the implementation of the provisions contained in the March 2013 Agreement a further development of regional networks for the emergency management.

Management of inhibitors

The difference in HC organisations affects the laboratory facilities, such as performed test and availability of staff during working days as well as in weekends and holidays. In Italy, immune tolerance induction programs are regularly applied in all centers, and bypassing agents such as recombinant activated clotting factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) are regularly used[30]. However, some children have to move to the largest HCs to receive central venous access device or have AV fistula created[31].

No financial constrain is affecting the inhibitors management until now.

Education and research

In Italy the number of thrombosis and haemostasis specialist has decreased as in other countries[32]. It is essential to promote specific actions in the universities, to foster training of healthcare professional in this area and guarantee the continuity of care.

Conclusions

Due to the different organisational models across the Regions, in Italy the pharmacological treatment is accessible in all regions, but wide differences are present for the availability of multidisciplinary services and for the laboratory facilities.

The March 2013 Agreement application should improve this situation, as it defines services that should be offered and an essential list of laboratory tests that should be available all day round.

To improve accessibility to home treatment and emergency care at the regional level, a Co-ordination Group should be established with the aim of identifying and tackling the actual gaps and define the appropriate organisation.

Following the experience of the Institutional Accreditation Model[11,12], we believe that the participation of non-governmental organisations, such as national or regional haemophilia patients' organisations, can bring an added value to the policy making process, including the product procurement process. An early involvement of PWH representatives in the discussion of any clinical or organisational guideline, as well as of any associated health care program, should be systematically pursued in line with the fourth principle of the EPHC[8], as in Emilia-Romagna Region where the structured involvement of patient organisation for the last 13 years has contributed to produce a well established and effective organisation of care for PWH.

Finally, we envisage the establishment of a central organisation, involving all key stakeholders (FedEmo, AICE, Regions and national institutions such as MoH, NBC, National Medicines Agency, etc) with the mission to promote the standardisation of haemophilia care across the Country, by overseeing the implementation of the March 2013 Agreement provisions and by monitoring the replacement therapy supply and costs. We also believe that the Italian national network for HCs, in compliance with European Union Committee of Experts on Rare Diseases (EUCERD)[33] and European Haemophilia Network project (EUHANET)[34] recommendations, should benefit of dedicated resources in order to be put in place. Therefore, among the tasks assigned to such central organisation, it would

be desirable foreseeing the commitment to advance proposals on funding mechanism for the HCs Network.

Keywords: haemophilia, Comprehensive Care Centre, Haemophilia Treatment Centre.

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