Current status of Italian Registries on inherited bleeding disorders

Hamisa Jane Hassan[1], Massimo Morfini[2], Domenica Taruscio[3], Francesca Abbonizio[1], Adele Giampaolo[1], Yllka Kodra[3], Emily Oliovecchio[2], Luciano Vittozzi[3]

[1]Section of Transfusion Methodologies, Department of Haematology, Oncology and Molecular Medicine, Italian National Institute of Health, Rome; [2]Italian Association of Haemophilia Centres (AICE), Florence, [3]National Centre for Rare Diseases, Italian National Institute of Health, Rome, Italy

Introduction

Inherited bleeding disorders are a group of congenital coagulopathies resulting when deficiencies of the proteins responsible for coagulation, platelet function or fibrinolysis occur. Haemophilia A (HA, deficiency of factor VIII), Haemophilia B (HB, deficiency of factor IX) and von Willebrand Disease (vWD) are the most frequent, being >90% of all inherited bleeding disorders with a prevalence of 0.5, 0.1 and 1-5/10,000 respectively[1-3]. Other rare inherited bleeding disorders are represented by deficiencies of factor I, II, V, VII, X, XI, XII, XIII, combined V+VIII, combined vitamin K-dependent factors, with a general population prevalence between 1/500,000 and 1/2,000,000[4]. Inherited bleeding disorders require wide-ranging care and effective management within a multidisciplinary team setting. The modern treatments of inherited bleeding disorders are now remarkably effective, although expensive.

In Italy the epidemiological data on inherited bleeding disorders derive from three registries:

1) The Italian National Registry for Rare Diseases (RNMR);
2) The National Registry of Congenital Coagulopathies (RNCC);
3) The Haemophilia Database of the Italian Association of Haemophilia Centres (AICE).

These registries differ in terms of organisation, purpose and data collection process. A general description and results for each registry is reported as follow.

Italian National Registry for Rare diseases

Organisation

The Italian National Registry for Rare Diseases has been established by law in 2001 (Ministerial Decree -M.D. n. 279/2001)[5], and it is located at the National Centre for Rare Diseases (NCRD) of the Italian National Institute of Health (Istituto Superiore di Sanità - ISS). M.D. n. 279/2001 set up a specific Rare Disease (RD) network dedicated to the prevention, surveillance, diagnosis and treatment of RD patients, set out special rules for the assistance of RD patients and ensured that health services are appropriately delivered to RD patients. The "RD Network" is made of formally designated Centres by each Italian region (FDC), preferably based in hospitals and dedicated to the management, care, training and information of RD patients and research on RD. This network provides data to the RNMR.

The mandate of the RNMR is to inform the national and regional planning of RD patient care and to collect demographic, history, clinical, laboratory determinant data of use for medical, biomedical and epidemiological research.

The structure of the RNMR is made of three levels, reflecting the Italian Healthcare System: local, regional and national level. The local level is composed by FDC identified in each Region, which are the primary source of data flow. Clinicians of FDC collect demographic and clinical data and transmit them to the regional registries. This is the intermediate level of data flow. Each regional registry has different organisational structure, different objectives or aims, and as a consequence different types of information (variables) to be collected. The use of the RNMR central data repository and the related common data set for the communication of mandatory data from the regional registries to the RNMR was defined with two Agreements among State and Regions in 2002 and in 2007. This set includes socio-demographic as well as disease information of each case: encrypted patient identification code, date of birth, sex, region of residence; vital status (with decease date); diagnosis; RD centre which made the diagnosis; date of disease onset; date of diagnosis; orphan drug treatment. This data set is mainly devoted to monitor RD and RD services at national level. RNMR data are presented and discussed annually in the national meeting of the RNMR and regional RD registries and the production of annual reports has started in 2011[6].

The RNMR monitors 495 conditions, including individual RD and groups of RD, which are listed in the technical annex to M.D. n. 279/2001. In particular, the following specific conditions of inherited bleeding disorders are under surveillance: inherited bleeding disorders, HA, HB, vWD, inherited deficiency of coagulation factors and platelets.

Results

Up to 30 June 2012, a total of 11,135 notifications on inherited bleeding disorders have been collected at RNMR: 7,748 for inherited bleeding disorders; 1,809 for inherited disorders of platelets; 615 for HA; 503 for inherited deficiency of coagulation factors; 367 for vWD and 93 for HB. Cases ≤18 years represent 13%.

Considerations

The RNMR is a population-based/multi-diseases registry and consequently an important instrument of public health, useful for health planning and epidemiological surveillance.

The strong legal base of the RNMR and the compliance with the national legal and ethical requirements ensures stability to the data collection. The future directions of RNMR are also to support the development of further clinical registries on specific RD, in order to better understand the natural history of RD. In fact the NCRD participates actively in a number of collaborative efforts with patient associations and networks of clinicians for the collection and exchange of patient data for specific RD registries; inherited bleeding disorders are the subject of a collaboration with the RNCC. Moreover the RNMR provides important indicators of accessibility of health care and health service utilisation by patients with RD.

The RNMR is now implemented in all the Regions but data quality and completeness still need to be improved. Indeed, the collaboration with different registries has shown that case notification is far from being complete, with considerable variation of notification rate across the Italian territory. Moreover, the notification of inherited bleeding disorders in RNMR uses a non specific terminology, which should be updated to allow sounder epidemiological observations.

The National Registry of Congenital Coagulopathies

Organisation

In Italy, haemophilia patients and other persons with inherited bleeding disorders are monitored by the RNCC established at the ISS with the collaboration of AICE.

Since 1988 until 1999, at ISS was activated a Registry aimed in particular to the surveillance of infectious diseases in the haemophiliac population, that, at the time, represented the most serious adverse event in the replacement therapy of inherited bleeding disorders[7,8]. After 1999 and so far, the RNCC has been fed by AICE Database.

Since 2005 a section of the Haematology, Oncology and Molecular Medicine Department is in charge of the management of the RNCC: collection, validation, elaboration and dissemination of the data. The RNCC was resumed as a specific pathology registry, in a stringent collaboration with AICE, the Haemophilia Treatment Centres (HTC) and the Patient's Association (FedEmo). The epidemiological surveillance of population with inherited bleeding disorders, treatment-related complications and monitoring of needs/consumption of products utilised in the different regimen therapies are the main aims of the RNCC[9-11].

Data collected in the RNCC are relative to all the 53 Italian Haemophilia Centres, established by Regional laws, and distributed in the North (49%) Centre (17%) and South and Islands (34%). They assist the Italian patients with bleeding disorders with a coverage of almost 100% of the severe forms. The participation of the HTC to the RNCC data collection is on voluntary basis. Data are provided from the local databases to the national database anonymised and in accordance with the Italian privacy law and standards.

Information collected in the RNCC are relative to 9,097 validated patients with HA and HB, vWD, other rare factor deficiencies (fibrinogen and factors II, V, VII, X, XI, XII, XIII inherited deficiencies), inherited platelet disorders and haemophilia carriers.

Data are relative to prevalence of inherited bleeding disorders, treatment-related complications (infectious diseases and in particular inhibitor development), needs/consumption of plasma-derived and recombinant products utilised in the haemophilia replacement therapy. These variables are available at national and regional level, by age group and by treatment regimen (prophylaxis/on demand/immune tolerance induction).

Haemophilia facilities, addresses, contact numbers and referents of the Centre are indicated and described in the appendix of the RNCC[9].

Data collection is possible through a software, now substituted by a web-based system, developed and distributed by AICE to the HTC to assist patient management. ISS strongly supported the AICE Database and can access to the information sent by the HTC being identified by AICE as the national organisation responsible for the elaboration and diffusion of the inherited bleeding disorders data.

Information collected are analysed and validated through a data quality control system aimed to check the quality of data entry and type of information. In case of data not compliant the referent of the Centre is asked to check the information provided for ensuring the consistency and completeness of patient information housed.

Since 2007, ISS has activated a specific questionnaire realised on the basis of the therapeutic treatment plans that represent the most reliable tool for monitoring the consumptions[12]. In fact therapeutic plans establish the products and doses to be used by patients during the year

and are necessary to receive therapy free of charge by the national public health service. Regimen and products are defined on a case by case and after informed consent and sharing between the specialist and the patient.

This direct data flow on treatment product consumption with the Haemophilia Centres allows to monitor the needs/consumptions of plasma-derived and recombinant products necessary for the haemophilia replacement therapy[12].

Data analysed and elaborated by ISS are published in an annual technical report (ISTISAN Report) distributed to the National and Regional administrators and to the HTC that contributed to data collection. RNCC is also published on the website of the ISS (www.iss.it). Since 2006, the RNCC has been included in the National Statistic System (SISTAN) that monitors the surveys of public interest and it is regularly published on the SISTAN website (www.sistan.it).

Moreover RNCC data are disseminated in the national meetings relative to rare diseases, published on international journals and also provided for the enquires of the Italian Health Ministry and Parliament.

Results

Patient number/Centre, pathology severity, age, gender, treatment regimen and annual product consumption/patient are the main markers utilised in the data analyses.

In 2012 the total number of validated patients included in the RNCC was 9,097, in particular 3,696 with HA (46% with severe HA), 744 with HB (37% with severe HB), 2,212 with vWD (4% with the severe type 3), 1,524 with other rare deficiencies (39% factor VII and 24% factor XI deficiencies). In 2012, the Italian prevalence of HA and HB was 6.1/100,000 inhabitants and 1.2/100,000 inhabitants, respectively.

The severe HA patients were 1,698 in total; 18% of these was registered as previously or currently positive to inhibitor. The incidence of inhibitor in severe HA patients was about 30% in 0-2 years.

The estimated amount of factor VIII utilised in the HA replacement therapy and factor IX for the HB therapy was 450,000,000 of International Units (IU) and 55,000,000 of IU respectively; in both cases 80% was represented by recombinant products.

Considerations

The Word Federation of Haemophilia (WFH) recommends the development of national patient registries through the collaboration between national patient organisations, healthcare professionals, treatment Centres and ministries of health[13]. The availability of a pathology specific Registry at national level improves the knowledge of the disease in terms of epidemiology, correlated diseases, care requirements, resources and new therapeutic strategies. The Italian RNCC corresponds to the requirements of the WFH allowing to provide reliable Italian data to international database.

There is the need to have a more efficient registration system in order to eliminate any redundancy in patient records and to make data collection in real time. Data collection, in particular on home therapy, requires the primary collaboration of the Patient's Association. The absence of specific national regulation and funding for the improvement of the RNCC is a limit that should be overcome.

The Haemophilia Database of the Italian Association of Haemophilia Centres

Organisation

The Haemophilia Database was developed within the AICE since 2003, in accordance with the main objectives of AICE to prompt optimal health care delivery through the Italian HTC, basic and clinical research and collection of epidemiological data on inherited bleeding disorders[14]. It is completely doctor-run and it is characterised by a voluntary nature about the contribution in activities of HTC directors, joined in AICE. Data on patients with haemophilia and allied bleeding disorders are regularly collected twice a year. AICE is the owner of the Haemophilia Database. Furthermore AICE has identified the ISS as the national organisation in charge of the analysis and the diffusion of the epidemiological data.

Management software is employed by HC directors for the data collection of Haemophilia AICE Database. In 2009 the software has migrated to the web, becoming web-based (EmoWEB) to improve accessibility, maintenance and security of users and data. EmoWeb was also designed to support all the daily activities of HTC and covers all the relevant fields of haemophilia management, in order to use it as computerised medical record.

Every 6 months each HTC director authorises patient data extraction through an automated procedure that anonymizes those records.

The Haemophilia AICE Database is regularly updated with information on patient demographics, clinical and laboratory phenotypes; after each update an automatic procedure creates local and national hyper textual reports. The local reports are related to patients treated in each HTC.

The national report displays all national data collected and discloses the Italian situation of haemophilia and bleeding disorders. All these reports are published in password-protected pages on the AICE website to allow HTC directors to check and validate the local reports; tables with summary data about Italian patients with

inherited bleeding disorders are also published in a public zone of the AICE website (http://www.aiceonline.it/emocard/homeRN.htm).

Moreover Haemophilia Registry data are disseminated during the AICE meeting and used for AICE research projects. Data are also provided by the technical reports published at the ISS.

Results

Database is filled by 53 HTC, distributed in the country. Since 2003 a total of 11,436 patients were collected, 10,444 after duplicate exclusion. In 2012 9,345 are living patients, 40% with HA, 8% with HB, 24% with vWD and 28% with other bleeding disorders.

The percentages of severe, moderate, and mild HCV-infected -HA patients are 45%, 37% and 20% respectively. The percentages of severe, moderate, and mild HCV-infected -HB patients are 38%, 27% and 12% respectively. The percentages of HIV infected patients are: 10% of severe, 4% of moderate, 0.5% of mild HA and 15% of severe, 5% of moderate, 0.6% of mild HB.

Considerations

The Haemophilia AICE Database, monitoring the data transmission from each HTC on patients with haemophilia and other congenital bleeding disorders, allows to check the HTC participation to the Database and to evaluate the homogeneity of the patient haemophilia management at national level.

The same guidelines followed by the Centres allow to collect harmonised data useful to address clinical studies. Therefore, the Haemophilia AICE Database represents a tool aimed to the implementation of important retrospective and prospective clinical and scientific studies on specific topics such as cancer, quality of life and mortality of haemophilia patients[15-18]. The goal of these studies is to better understand some specific aspects on the haemophilia and bleeding disorders management and to provide more focused recommendations for treatment and follow-up.

Conclusions

The RNMR, the RNCC and the Haemophilia AICE Database monitor inherited bleeding disorders and are already well established, they have many commonalities but many disparities at the same time (Table I).

The primary source of data collection for the RNMR and RNCC is different. The data sources of the RNMR are FDC, established by regional law and dedicated to

Table I - Comparative data on the bleeding disorders data flow (2012).

	National Registry for Rare Diseases (RNMR)	National Registry of Congenital Coagulopathies (RNCC)	Italian Association of Haemophilia Centres (AICE) Database
Institution	By law	Voluntary	Voluntary
Organisation	Governmental National Institute	Governmental National Institute	Scientific Society
Data flow	Local Centres of Reference - Regional Registries- National RNMR	Local Haemophilia Centres - AICE Database - National RNCC	Local Haemophilia Centres - AICE Database
Purpose	Rare diseases surveillance	Inherited bleeding disorders surveillance and drug consumption monitoring	Clinical and scientific studies on inherited bleeding disorders
Data collected			
Severe Haemophilia A	No	Yes	Yes
Moderate Haemophilia A	No	Yes	Yes
Mild Haemophilia A	No	Yes	Yes
Total Haemophilia A	Yes	Yes	Yes
Severe Haemophilia B	No	Yes	Yes
Moderate Haemophilia B	No	Yes	Yes
Mild Haemophilia B	No	Yes	Yes
Total Haemophilia B	Yes	Yes	Yes
von Willebrand Disease (type 1)	No	Yes	Yes
von Willebrand Disease (type 2)	No	Yes	Yes
von Willebrand Disease (type 3)	No	Yes	Yes
Total von Willebrand Disease	Yes	Yes	Yes
Deficiency of other coagulation factors	Yes	Yes	Yes
Inherited thrombophilic disorders	Yes	No	No
Platelet disorders	No	Yes	Yes
Inherited bleeding disorders	Yes	Yes	Yes
Drug consumption monitoring	No	Yes	No
Total inherited bleeding disorders	11.135	9.097	9.345

the management of RD; data for the Haemophilia AICE Database and the RNCC derive from the Italian HTCs, established by regional law and assisting the Italian patients with bleeding disorders.

The completeness of the ISS registries is different; in particular the prevalence of HA and HB, estimated by the RNMR, is much lower than that reported in the RNCC. This underreporting probably depends on the RNMR terminology, in fact the most of patients with HA and HB are notified as patients with inherited bleeding disorders, without specifying which bleeding disorder. Furthermore not all FDC follow patients with bleeding disorders and are active in sending the relative data.

The epidemiological data about patients with bleeding disorders, collected in the Haemophilia AICE Database and the RNCC, are more homogenous than that collected in the RNMR because the HTC represent the principal data source for both data collection.

The RNMR, the RNCC and the Haemophilia AICE Database are not fully interoperable between them because of different patient identification code and terminology codification. Interoperability procedures should be developed in order to obtain data sharing through standard terminology classification and to exchange agreed and harmonised data.

The aim of both the ISS registries is patient care and public health oriented. The RNMR is a multi-diseases registry, containing 495 rare diseases; every class of pathology should be further investigated through the institution of specific disease Registry. The RNCC, investigating the inherited bleeding disorders, allows a specific analysis of this group of pathologies and could represent a model for the institution of other disease Registries.

The European Commission Communication: "Rare diseases: Europe's challenge", the subsequent Council Recommendation[19,20] and the WFH emphasize the strategic importance of Patient Registries and the development of similar specific registries can be beneficial also for the knowledge of other rare pathologies.

The AICE Database is managed by the scientific association of Haemophilia Centres and is a research oriented instrument providing data for prospective clinical studies; epidemiological data are shared with the ISS for the progress of the RNCC to which AICE strongly cooperates.

Keywords: registries, rare diseases, inherited bleeding disorders, haemophilia.

Authorship contribution

Hamisa J. Hassan, Massimo Morfini and Domenica Taruscio contributed equally to the paper. Hamisa J. Hassan, Massimo Morfini and Domenica Taruscio are responsible for i) the National Registry of Congenital Coagulopathies, ii) the Haemophilia Database and iii) the National Registry for Rare Diseases, respectively.

Hamisa J. Hassan, Massimo Morfini and Domenica Taruscio conceived the review.

Francesca Abbonizio, Adele Giampaolo, Yllka Kodra, Emily Oliovecchio and Luciano Vittozzi analysed the data and were involved in writing.

The Authors declare no conflicts of interest.

References

1) Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Reviews 2013; **27**: 179-84.
2) Mannucci PM. Treatment of haemophilia: building on strength in the third millennium. Haemophilia 2011; **17**: 1-24.
3) Castaman G, Goodeve A, Eikenboom J on behalf of the European Group on von Willebrand disease (EUvWD). Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica 2013; **98**: 667-74.
4) Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood 2004; **104**: 1243-52.
5) Decreto18 maggio 2001, n. 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124. (GU n. 160 del 12-7-2001-Suppl. Ordinario n.180/L). Available at: http://www.iss.it/binary/cnmr/cont/DM279-2001.1205943575.pdf. Accessed on 15/11/2013.
6) Taruscio D. Il Registro Nazionale e i Registri Regionali/interregionali delle Malattie Rare. Rapporto anno 2011. (Rapporti ISTISAN 11/20). Roma: Istituto Superiore di Sanità; 2011. Available at: http://www.iss.it/publ/index.php?lang=1&id=2529&tipo=5. Accessed on 15/11/2013.
7) Ghirardini A, Schinaia N, Chiarotti F, et al. Registro Nazionale delle Coagulopatie Congenite in Italia. Rapporto 1990. (Rapporti ISTISAN 91/33). Roma: Istituto Superiore di Sanità; 1991. Available at: http://www.iss.it/publ/index.php?lang=1&id=780&tipo=5. Accessed on 15/11/2013.
8) Ghirardini A, Puopolo M, Mannucci PM, et al. Registro Nazionale dell'Emofilia del Gruppo Italiano Coagulopatie Congenite (GICC): Rapporto 1993. (Rapporti ISTISAN 94/13). Roma: Istituto Superiore di Sanità; 1994. Available at: http://www.iss.it/publ/index.php?lang=1&id=688&tipo=5. Accessed on 15/11/2013.
9) Abbonizio F, Giampaolo A, Arcieri R, et al. Registro Nazionale delle Coagulopatie Congenite. Rapporto 2011. (Rapporti ISTISAN 12/55). Roma: Istituto Superiore di Sanità; 2012. Available at: http://www.iss.it/publ/index.php?lang=1&id=2681&tipo=5. Accessed on 15/11/2013.
10) Abbonizio F, Giampaolo A, Calizzani G, et al. Registro Nazionale delle Coagulopatie Congenite. Rapporto 2008. (Rapporti ISTISAN 10/31). Roma: Istituto Superiore di Sanità; 2010. Available at: http://www.iss.it/publ/index.php?lang=1&id=2439&tipo=5. Accessed on 15/11/2013.
11) Abbonizio F, Giampaolo A, Palmieri S, et al. Registro Nazionale delle Coagulopatie Congenite. Rapporto 2006-2007. (Rapporti ISTISAN 08/46). Roma: Istituto Superiore di Sanità; 2008. Available at: http://www.iss.it/publ/index.php?lang=1&id=2269&tipo=5. Accessed on 15/11/2013.

12) Giampaolo A, Abbonizio F, Puopolo M, et al. Consumption of clotting factors in severe haemophilia patients undergoing prophylaxis and on-demand treatment in Italy. Transfus Med 2011; **21**: 280-4.
13) Evatt BL, Black C, Batorova A, et al. Comprehensive care for haemophilia around the world. Haemophilia 2004; **10**: 9-13.
14) Iorio A, Oliovecchio E, Morfini M, et al. Italian Registry of Haemophilia and Allied Disorders. Objectives, methodology and data analysis. Haemophilia 2008, **14**: 444–53.
15) Tagliaferri A, Di Perna C, Santoro C, et al. Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers. J Thromb Haemost 2012; **10**: 90-5.
16) Tagliaferri A, Rivolta GF, Iorio A, et al. Mortality and causes of death in Italian persons with haemophilia 1990-2007. Haemophilia 2010; **16**: 437-46.
17) Tagariello G, Iorio A, Santagostino E, et al. Comparison of the rates of joint arthroplasty in patients with severe factor VIII and IX deficiency: an index of different clinical severity of the 2 coagulation disorders. Blood 2009; **114**: 779-84.
18) Rocca A, Pizzinelli S, Oliovecchio E, et al. Replacement therapy with recombinant factor IX. A multicentre evaluation of current dosing practices in Italy. Blood Transfusion 2010; **9**: 60-9.
19) Communication from the Commission to the European Parliament, the Council, the European economic and social committee and the committee of the regions on rare diseases: Europe challenges. Commission of the European Communities. Available at http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf. Accessed on 15/04/2013.
20) Council Recommendation of 8 June 2009 on an action in the field of rare diseases. The Council of the European Union. Available on line at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF. Accessed on 23/08/2013.

Correspondence: Hamisa J. Hassan
Department of Haematology, Oncology and Molecular Medicine
Italian National Institute of Health
Viale Regina Elena 299
00161 Rome, Italy
e-mail: jane.hassan@iss.it