Thrombosis Research 127 Suppl. 2 (2011) S22–S25

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

EUHASS: The European Haemophilia Safety Surveillance system

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ARTICLE INFO

Keywords:
Haemophilia
Adverse events
Inhibitor
Thrombosis

ABSTRACT

Pharmacovigilance is an essential element of any drug treatment and considering the history of adverse events due to products used to treat inherited bleeding disorders, it should be an integral component of modern haemophilia treatment. Because inherited bleeding disorders and adverse events are rare, a multicentre, preferably multinational, adverse event reporting scheme for all clotting factor products is required. EUHASS is a European, prospective, multicentre adverse event reporting scheme in the field of inherited bleeding disorders.

Introduction

The mainstay of treatment of inherited bleeding disorders is through replacement of the missing clotting factor, largely prepared from pooled plasma and more recently through recombinant technology for some disorders. Because these products were not initially virally inactivated, large numbers of recipients were infected in the early 1980s with hepatitis B and C as well as HIV [1]. Viral inactivation virtually eliminated this infective risk but problems with adverse events related to concentrates remain, especially in the areas of allo-antibodies to FVIII (inhibitors) and increasingly with regard to thrombosis, including cardiovascular disease, as the population being treated is getting older. It is important to remain alert to the possibility of adverse events due to current treatments of this patient group [2].

Pharmacovigilance is a term used to describe the detection, monitoring and investigation of adverse drug reactions and it is performed in two main ways. Firstly through voluntary reporting by health professionals and patients to the regulatory authorities and secondly by the manufacturers as part of the regulatory process. Both processes, however, have limitations and clinicians may not report all events promptly because they are busy, they may not be aware of the schemes available for reporting, they may believe that the adverse event is well known or not serious enough to report, and they may not wish to report suspicions until they are certain of the association. Reporting from manufacturers during clinical trials tends to be from very small groups of selected patients [3].

As inherited bleeding disorders are very rare [4], it is clear that a pharmacovigilance program will need to be multicentre, probably multinational, simple and comprehensive so all the bleeding disorders are covered. It is against this background that the European Haemophilia Safety Surveillance (EUHASS) Pharmacovigilance program was set up.

Outline of the system

The EUHASS system accepts reports of adverse events from participating centres electronically. The current system is only available in English. Initially 43 sentinel centres agreed to take part and surveillance began on 1st October 2008 but as the program has continued other centres have joined and currently there are 64 participating centres (Table 1). Once centres have obtained ethical clearance they are provided with a unique username and password that enables them to access the internet-based system and report their adverse events. Events can be reported as they occur or as a minimum at the end of every three-month surveillance period. Reporting is anonymous using the Soundex coding system. The same surname will always produce the same Soundex code and it is not possible to work out the patient's surname from the Soundex code. This way of reporting avoids duplicate reporting of events if patients were to attend two participating centres. (At present because the number of centres in each country is small, the possibility of attendance by patients at two participating centres is

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Table 1
Centres participating in the EUHASS study as of 1st October 2010

Country	Centre(s)
Austria	Vienna – adults, Vienna – children
Belgium	Brussels, Leuven
Bulgaria	Sofia
Cyprus	Nicosia
Czech Republic	Brno – adults, Brno – children, Prague
Denmark	Aarhus, Copenhagen
Finland	Helsinki
France	Lille, Lyon, Montpellier, Paris – Bicêtre, Paris – Necker
Germany	Berlin, Bonn, Bremen, Munich – adults, Munich – children
Greece	Athens – Aghia Sophia, Athens – Hippocration, Athens – Laikon
Hungary	Budapest
Ireland	Dublin
Italy	Castelfranco Veneto, Florence, Milan, Napoli, Parma, Perugia, Rome Catholic University, Vicenza
Latvia	Riga
Lithuania	Kleipeda
Netherlands	Rotterdam, Utrecht
Poland	Warsaw
Portugal	Lisbon, Porto – Santo Antonio, Porto – São João
Romania	Timisoara
Slovakia	Bratislava
Spain	Barcelona, Malaga, Valencia
Sweden	Malmö, Stockholm
Switzerland	Geneva, Zurich – children
Turkey	Istanbul, Izmir
UK	Aberdeen, Birmingham – adults, Edinburgh, Glasgow – adults, Glasgow – children, London – Hammersmith, London – Royal Free, Manchester – adults, Sheffield – adults, Sheffield – children

very small.) Annually centres report the number of patients with inherited bleeding disorders under their care by specific diagnostic category as well as the number of patients treated by a specific concentrate. The project started on 1st October 2008 and at the end of each 3-month period centres have three weeks to report their data so the three-monthly report is produced within four weeks of the end of each surveillance period. Every 12 months more detailed analysis is provided and this includes inhibitor rates for each concentrate.

Organisational structure

The EUHASS project is coordinated from the University of Sheffield by Dr Mike Makris and the main partners are the University of Milan, the University Medical Center Utrecht, the European Haemophilia Consortium (the patients' organisation) and the UK Haemophilia Centre Doctors' Organisation Ltd. Centres taking part in EUHASS become subcontracted partners by signing a short subcontract as formal agreement to project deadlines for submission of data. A steering committee consisting of PM Mannucci, M Makris, G Calizzani, K Fischer, CRM Hay, T Lambert, R Lassila and CA Ludlam oversees and directs the project.

Events being reported

The following events are reported to EUHASS either as they occur or on a three-monthly basis:

(a) Acute or allergic events. New events that the participating centre feels may be related to the treatment are reported. As well as describing the event and providing details of outcome, reporters are asked to indicate how likely they feel it is that the event was due to the treatment product.
(b) Transfusion-transmitted infections. As well as collecting details of new classical transfusion-transmitted infections, e.g. hepatitis B, hepatitis C and HIV, participants are able to report other infections which they suspect may have been transmitted by the clotting factor treatment.
(c) Inhibitors. In the first year of EUHASS only new inhibitors were accepted, however from year 2 recurrent inhibitors were also accepted. Recurrent inhibitors are reported and analysed separately from inhibitors occurring the first time. Inhibitors are only accepted when detected at any titre above the laboratory normal limit on two separate occasions. In the case of recurrent inhibitors the time of the last negative test is also reported.
(d) Thromboses. New episodes of myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis are accepted. Also reported prospectively are the first-ever episodes of angina pectoris and transient ischaemic attacks. For each reported episode details of the circumstances, e.g. if post-operative or related to a central venous access catheter, as well as the presence of classical risk factors for thrombosis are also reported. Thromboses are presented in two groups depending on whether they occurred within or after 30 days post concentrate administration.
(e) Malignancies. Only new first malignancies are reported, recurrences of previous malignancies or new metastases are excluded. The hepatitis and HIV status of each patient with a new malignancy as well as exposure to radioactivity during synovectomy are also reported.
(f) Deaths. Deaths are reported for all patients in the surveillance program. Details of cause as well as whether an autopsy was performed and their hepatitis/HIV status are collected.

The adverse events reported must be new and must be reported prospectively. For each of the above reported events participants

provide information in three sections; firstly details of the patient such as age, diagnosis and severity, secondly details about the event including the product and batch numbers involved and thirdly additional questions about the outcome and presence of other risk factors. All information is readily obtained from standard patient management, with no extra patient examination or testing required.

Cumulative data being reported

At the end of every 12-month surveillance period participating centres provide cumulative data on the population surveyed in two formats.

Firstly, for each diagnostic category, e.g. haemophilia A, factor XI deficiency etc., centres provide data on the number of persons registered and followed up, the number who have severe disease, the number treated in the 12-month period with concentrate, FFP or cryoprecipitate as well as the number treated with one of the two bypassing agents, FEIBA or rFVIIa (used as an indirect measure of the presence of active clinically significant inhibitor). Severe disease is defined as <1% for haemophilia A and B according to the ISTH definition [5] but in the absence of a widely accepted definition for the other disorders we have used the <10% limit.

The second way centres report cumulative data is per product used. For each separate clotting factor concentrate, the centres report the total number of patients treated in the 12-month period. For the severe patients only, they also report total number treated, the number treated who are still under the 50 exposure day limit at the end of the surveillance period and the number who reached their 50th exposure during the surveillance year. The cumulative incidence of inhibitor development in previously untreated patients according to product is then calculated [by dividing the number of patients who developed inhibitors by the sum of the number of inhibitors and the number who reached 50 exposure days without inhibitor development]. The previously treated patients, defined as those severe haemophiliacs who reached their 50th exposure before the start of the surveillance year, are reported separately depending on whether they are continuing on the same concentrate or whether they switched to this product during the surveillance year.

Patients under surveillance

All patients with inherited bleeding disorders at the participating centres are included in the surveillance. For haemophilia only patients with <40% clotting factor levels are included as recommended by the International Society for Thrombosis and Haemostasis definition [5]. Female carriers are also included if they have FVIII or IX levels <40%. Patients with acquired bleeding disorders, e.g. acquired haemophilia A, are excluded. Patients with von Willebrand disease are included if they have type 2 or type 3 disease or if they have type 1 disease with <15% von Willebrand factor activity levels – the latter cut-off being selected as a level that will include most patients with the disease who may be treated with concentrates. Table 2 lists the diagnostic categories of included patients.

Table 2
Diagnostic categories included in the EUHASS project

Haemophilia A (<40% FVIII:C)
Haemophilia B (<40% FIX:C)
Von Willebrand disease – type 1 if VWF:RCo is <15%
Von Willebrand disease – all type 2 and 3
Afibrinogenemia (Fibrinogen <10 mg/dl)
Hypofibrinogenemia (Fibrinogen 10–50 mg/dl)
Dysfibrinogenemia (Fibrinogen 50–150 mg/dl)
Factor II deficiency
Factor V deficiency
Factor VII deficiency
Factor X deficiency
Factor XI deficiency
Factor XIII deficiency
Alpha 2 antiplasmin deficiency
Combined factor V and VIII deficiency
Combined factor II, VII, IX and X deficiency

Ethics approval and data security

Ethics regulations vary enormously throughout Europe and all participating centres comply with local regulations. Whilst in some cases full ethics approval was required, in other centres the ethics committee felt, after reviewing an outline of the project, that a full ethics application was not necessary. Centres are accepted to participate only after they have obtained local clearance from their ethics committee. The EUHASS data are owned equally by the doctors' organisation, the European Association for Haemophilia and Allied Disorders (EAHAD), and the patients' organisation, the European Haemophilia Consortium (EHC). The data are held on a dedicated server which has an uninterruptable power supply and RAID (redundant array of independent disks) configuration to prevent data loss due to hard drive failure. The server is housed in a dedicated secure room and all participating centres access the site via unique usernames and passwords. All data are transmitted from centres to the server using full SSL 128 bit encryption and a comprehensive rotational backup procedure is in place with physical backup media stored in a fireproof safe.

Information technology

The UKHCDO Ltd is the partner responsible for all the information technology aspects of the project. This partner has set up the EUHASS website and data entry site, provided the in-person and online training and continues to provide a rapid response to problem solving. A facility is available to connect to the participant's computer remotely and help them with any problems or queries.

Other activities

Website

The EUHASS system has a website which can be accessed at www.euhass.org. The site consists of a public area with information freely accessible to all, as well as a login area for participating centres only, through which they can access the secure data entry site and enter their surveillance data.

Haemophilia centre database

EUHASS has developed a database of all the haemophilia centres in Europe. This facility is freely available to the public from the main website. A powerful search engine allows the user to identify the centre they are looking for using a number of parameters. Currently there are 411 centres listed on the site. As well as showing the name, address and list of clinical staff at the centres, the telephone numbers and instructions of how to obtain haemophilia care during normal working hours and evenings and weekends are provided. The system is still under development and when complete it will be possible to find European Haemophilia Centres using Google maps.

Clotting factor database

The main website also contains a freely available database of all the clotting factor concentrates currently used in Europe. A

search facility allows identification of the required concentrate and lists many of its characteristics including plasma source and viral inactivation procedures. When complete the database will also contain abstracts and details of all the publications related to a specific concentrate. The full text of the articles will not be given but if they are freely available a link to the relevant site will be provided.

Rapid alert system

EUHASS has developed a system whereby haemophilia treaters can be rapidly informed of important developments in the area of safety. When a relevant event is identified, the steering committee convenes by telephone conference within 24 hours to discuss the issue. There are strict rules about how the conference is called and conducted and how it is decided when to issue a communiqué. The information is disseminated by email or fax to the directors of all the haemophilia centres whose details are available on the system. At the time of writing the Rapid Alert System has been activated only once to provide information about the identification of vCJD prions in the spleen of a haemophiliac in the UK [6].

Funding

The EUHASS system was set up following the award of a competitive grant from the European Union DG SANCO directorate which provides 60% of the total funding. The remaining 40% is provided by 9 pharmaceutical manufacturers who each give 4.4% of the total funding but have no influence on the design or execution of the project. The pharmaceutical partners are Baxter, Bayer, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma and Pfizer (formerly Wyeth).

Acknowledgements

We thank all the staff at the participating centres without whose help, enthusiasm and dedication this project could not succeed. Mr Enis Muminovic and Dr Rob Hollingsworth are responsible for the IT aspects of the project. We thank our funders outlined in the above section. This paper arises from the project EUHASS which has received funding from the European Union, in the framework of the Public Health Programme.

Conflict of Interest Statement

This study is partially funded by 9 pharmaceutical manufacturers as stated in the funding section of this paper.

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