The value of a European registry for pituitary adenomas: The example of Cushing’s syndrome registry

Intérêt d’un registre européen des adénomes hypophysaires : l’exemple du registre du syndrome de Cushing

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Abstract

In the field of Rare Diseases, patient registries and databases are key instruments for the development of clinical research, improvement of patient care and healthcare planning. They can achieve a sufficient sample size for epidemiological and/or clinical research, to assess feasibility of and facilitate planning of appropriate clinical trials, and support the enrolment of patients to be treated with orphan drugs. Registries of patients treated allow the gathering of evidence on the effectiveness of treatments and possible side effects, since marketing authorisation is often granted when evidence albeit convincing, is limited. The European Registry of Cushing’s syndrome (ERCUSYN) database initially funded by the EU, now includes data on over 500 patients. It represents the largest collaboration of endocrine centres in Europe and has potential not only for improving the care of patients with Cushing’s syndrome, but also to extend its collaboration into new areas. It may be used as a rare disease registry for an orphan drug to be evaluated, such as a new somatostatin analogue. This academic registry set up before marketing authorization of this new drug as a disease registry, may be liaised to a European Medicines Agency-regulated, industry-required post-marketing surveillance study, to follow safety and efficacy in the long term outcomes in clinical practice conditions. Through the ESE this network may be used to disseminate information and encourage further interaction between endocrinologists across Europe.

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Résumé

Dans le domaine des maladies rares, les registres de patients et les bases de données sont des instruments déterminants pour le développement de la recherche clinique, l’amélioration de la prise en charge des patients et la planification des soins. Ils permettent la constitution d’un échantillon de taille suffisante pour une recherche épidémiologique et/ou clinique afin d’évaluer la faisabilité et de faciliter la mise en place d’essais cliniques appropriés et pour être le support de l’inclusion de patients à traiter par des médicaments orphelins. Les registres de patients traités permettent d’accumuler des données sur l’efficacité des traitements et les effets secondaires puisque les autorisations de mise sur le marché sont souvent données alors que les arguments, même s’ils sont convaincants sont limités. Le registre européen du syndrome de Cushing (ERCUSYN) est une base de données qui a initialement reçu des fonds de la Communauté européenne et qui a inclus des données concernant plus de 500 patients. Il est l’illustration d’une collaboration majeure des centres d’endocrinologie en Europe et a le potentiel non seulement d’améliorer la prise en charge des patients ayant un syndrome de Cushing, mais aussi d’étendre sa collaboration dans de nouveaux domaines. Il peut être utilisé comme un registre de maladies rares pour l’évaluation d’un médicament orphan comme par exemple un nouvel analogue de somatostatine. Ce registre académique, mis en place en tant que registre des maladies avant l’autorisation de mise sur le marché de ce nouveau médicament, pourra aussi être utilisé pour une étude de surveillance postmarketing recherchée par l’industrie pharmaceutique et régulée par l’Agence européenne du médicament afin de suivre l’efficacité et la sécurité des conditions cliniques quotidiennes et sur le long terme. Via la Société européenne d’endocrinologie, ce réseau pourrait aussi être utilisé afin de disséminer l’information et encourager plus d’interactions entre les endocrinologues à travers l’Europe.

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1. Introduction

Patient registries and databases (DB) constitute key instruments to develop clinical research in the field of rare diseases (RD), to improve patient care and healthcare planning [1]. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research, and are vital to assess the feasibility of and to facilitate the planning of appropriate clinical trials, and to support the enrolment of patients to be treated with orphan drugs (Table 1). Registries of patients treated with orphan drugs allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing [2] (Table 2).

Rare diseases are a clinically heterogeneous group of about 6500 disorders, commonly diagnosed during childhood, often inherited, and can have deleterious long-term effects. Although any one condition is rare, their cumulative public health burden is substantial, with 6–8% of people having a rare disease at some point during life [3].

Because of the rarity, no single institution, and in many cases no single country has sufficient numbers of patients to do generalisable clinical and translational research. Geographic spread of patients has been a major impediment to recruitment into clinical trials. Often rare diseases do not have a specific International Classification of Diseases code, which hampers research that uses existing databases [3]. The European Union, and Asian countries passed orphan-drug legislation more than 20 years ago, but the drug industry gave little attention to the development of registries of patients treated with orphan drugs (Table 1). Registries of patients treated with orphan drugs allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing [2] (Table 2).

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In recognition of these barriers and the moral and public health imperatives to advance knowledge on the best ways to improve the health and wellbeing of patients with rare diseases, recent conferences and research programs in the USA [5] and Europe [6] called for greater access to registries for such patients [7]. Recent agreements both by the EU and US support the establishment of registries for research and Public Health purposes as one of the priorities for the call launched in 2011 by the International Rare Disease International Research Consortium (IRDIRC) [8].

The European Union Committee of Experts on Rare Diseases (EUCERD) with the support of the European Medicines Agency (EMA) has devoted efforts to ensure correct development and maintenance of databases. After reports on “Patient registries in the field of rare diseases” (2008/2011) [9] and “Health indicators for rare diseases (2010, 2011)” [2] as well as the Orphanet Report “Disease registries in Europe” (2011) [2], a workshop was organised in October 2011 in London. The outcomes of this workshop will serve as the basis for the elaboration of a EUCERD recommendation in this field and will be available online on the EUCERD web in 2012 [10,11]. Among the objectives were to avoid the duplication of work in this field, to maximise the output and discuss sustainability. A consensus was established amongst the gathered stakeholders that it is imperative that fragmentation of data sources be avoided. Public/private partnership is necessary and, although it cannot be made mandatory, it can be suggested by the EMA to companies that they should consider joining existing registration systems or establishing a new one in partnership with an academic team and patient organisations. This has actually occurred in the last year with ERCUSYN (European Registry of Cushing’s syndrome); a drug firm who was filing for an authorization for a new orphan drug was asked to contact ERCUSYN in order to guarantee long-term safety and efficacy in a post marketing surveillance study. Other suggestions are to provide technical and methodological support, as well as rules of conduct for such partnerships. Regulatory frameworks and standards must be assured and open-access to data should be promoted. Management by academia was identified as a solution for ensuring long-term sustainability with the financial support of the regulatory bodies and of the payers, jointly with the concerned companies.

In the US a recent book on “Registries for evaluating patient outcomes: A user’s guide” by the US Agency for Healthcare Research and Quality (AHRQ) is available online [12]. It contemplates a patient registry as an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure: It can serve a predetermined scientific, clinical, or policy purpose(s). They are considered a valuable complement to randomized controlled trials in determining real-world outcomes in the practice of medicine. In comparison to clinical trials they do not usually have restrictive inclusion or exclusion criteria, nor do they
specify what therapy should be prescribed. They can be used to evaluate outcomes for diverse purposes ranging from the natural history of a disease, to determine clinical effectiveness or cost effectiveness of health care products and services including safety of drugs or devices, to the real-world effectiveness of therapies, and/or to measure quality of care.

2. Characteristics of databases for rare diseases

Common issues when contemplating registries on RD include scarcity of cases and complexity of diseases, which impose the necessity of a large geographical coverage (European or international, rather than regional or national), with limited transnational resources and funding. Additionally, networks corresponding to the relationship existing between several databases (or patient registries) may coexist, with or without a coordinating database.

Accreditation of EU registries for RD has been considered by the EUCERD to favour cross-talk between activities of disease specific groups/academia/industry initiatives and public health programmes. This facilitates solutions and prevent more “reinvention of wheels”, addressing issues of partnerships, sustainability, credibility by facilitating communication by the structure of EUCERD with representation of Member States of the European Union, and ensures that there is not any duplication of effort but rather embed RD registries in overall planning. Clinicians are not usually epidemiologists but expertise in both fields is necessary to optimise opportunities. As opposed to drug registries, disease registries tend to be favoured nowadays since they permit a better knowledge of natural history and clinical validity of new drugs in clinical practice conditions.

Orphanet, a reference European information portal on RD and OD, established first in France in 1997, is currently used worldwide and available in 36 European countries and 6 languages. It aims to improve diagnosis, care and treatment of all levels related to RD. It currently includes information on 6000 RD, nearly 800 drugs, 2000 patient associations, 15 000 health professionals and 5000 specialized centres on diseases with a low prevalence. Its web receives some 12.000 hits per day. Some of its recent reviews [2,9–11] show that most available registries are national and run by academic institutions (95 %, 490/514), while less than 5 % are run by private companies (3 %, 16/514) or patients organizations (< 2 %, 8/514). By medical areas, the most common registries in Europe are devoted to Neurology (21 %), Oncology (19 %) inborn errors of metabolism (8.5 %), while Endocrinology accounts for 6 % of registries, in parallel to Nephrology and Systemic and Rheumatologic diseases. However, less than a fifth of rare diseases have registries [6]. A few international registries (eg. in cystic fibrosis) [13] and neuromuscular diseases [14] are showing the benefits of combining data across international boundaries.

3. Utility of rare disease databases

Rare Disease Databases may constitute a communication means for academics and ethical committee members of international bodies like the EMA/EUCERD, to support public/private partnership in collaborating for post-marketing surveillance and in the development of further registries. They may also generate the development of guidelines on the requirements for research ethics committees in each member state and the off label use of drugs (i.e., the use of ketokonazole for the medical treatment of Cushing’s syndrome). They contribute to avoid duplication of efforts so as not to waste resources and expertise in a field where the latter are scarce, and to provide unified sources of data for diseases where several products are available.

Eurordis (Europe Rare Diseases), the voice of Rare Disease patients in Europe also promotes registries for RD, since they contribute to ease and speed up clinical research in the field of RD and OD, and provide data to regulatory bodies, to bodies in charge of assessing the Clinical Added Value of Orphan Drugs and to reimbursement bodies (Table 1).

Disease registries play an important part in improving health outcomes. They can also reduce the costs of health care. Through the use of such registries, health-care providers can compare, identify, and adopt best practices for patients. The Swedish Government is committed to increasing its annual financial support for disease registries from $10 million to $45 million by 2013 [15].

Since pharmacovigilance in rare diseases has many challenges (i.e., very limited knowledge of safety profile at authorisation, insufficient knowledge on the epidemiology of the disease, very few patients in one country, treatment with multiple drugs), registries are a valuable resource in orphan drug pharmacovigilance and risk management. The European Medicines Agency (EMA) is trying to increase research capabilities in Europe through the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), for which collaboration is essential. ENCePP is an EMA-led project bringing together expertise in the fields of Pharmacoepidemiology and Pharmacovigilance scattered across Europe, to strengthen further the post-authorisation monitoring of medicinal products in Europe and facilitate post authorisation studies of high quality, independent and multi-centre. ENCePP Database of Resources offers information available to the general public [16], sources of expertise and research experience, for both study sponsors and researchers seeking to identify collaborations in pharmacoepidemiology and pharmacovigilance studies in Europe. Advantages of Registries in Orphan Pharmacovigilance include that it may be the only practical way of collecting information on patients with rare diseases, can allow further information on epidemiology of the disease, with more knowledge of the short term safety profile and long term safety and efficacy data of the medicine, allowing comparison of medicines used to treat the disease, for which it may require to collect information from multiple centres and international co-operation (Table 2).

4. Requirements of a database for rare diseases

It is now considered to be the time to design and develop the infrastructure to foster global rare-disease registries. The increasing mobility of populations and the globalisation of lifestyles and food products make it clear that disease knows no boundaries [17]. Some rare diseases occur so infrequently
(<1 per 1 000 000 population) that only by forming international populations can sufficient numbers of patients be accrued. Because funding has been a key obstacle to establishing and maintaining registries, global rare-disease infrastructures would improve access to registries for many patients.

It is always necessary to attain a compromise between quantity and quality. In other words, it is usually recommended to collect the essentially necessary data, but being too demanding on quantity of data usually ends up in a significant proportion of incomplete databases with the consequent decrease in quality. Data should be introduced in a simple and intuitive way, since if not partners will lose motivation, when screens are unclear or complicated; there should also be mechanisms to prevent the introduction of “impossible” results (in order to detect errors, i.e. wrong units or anthropometry or hormone values). A clear manual easily accessible is a must, with a clear indication of “required fields”, without which further data cannot be introduced. The cost of developing and maintaining a database is a real concern, and also who is going to pay for it. It should be realized that registries often serve multiple purposes, which may change over time (Table 3).

Another essential question is quality control and validation of the introduced data, to confirm that the data were collected in accordance with established procedures and that they meet the requisite standards of quality to accomplish the registry’s intended purposes and the intended use of the data. Although all registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than others. Recruitment and retention of registry sites and patients are essential to the success of a registry. Factors that motivate participation include the perceived relevance, importance, or scientific credibility of the registry, as well as the risks and burdens and any incentives for participation. To date, no standards have been developed by which to guide evaluation of registries, and the research into quality aspects of registries has been sparse. There are two major difficulties with assessing quality in registries. On the one hand, it can often be difficult to differentiate between the quality of the design, the study conduct, and the information available; on the other, there is a lack of empirical evidence for evaluating parameters that indicate quality and impact on the evidence produced from registries.

Registries may be very useful vehicles for providing clinically relevant real-world information, even when they meet relatively few of the basic elements of good practice (typically because of budgetary limitations). In many cases, some data are better than no data, and even registries that fall short of including all the basic elements of good registry practice may still provide valuable insights about real-world medical and consumer practices and disease etiology. For example, a disease-specific registry that has been designed to look at natural history should not be deemed low quality simply because it is not large enough to detect rare treatment effects. Evaluations of the quality of any registry must take into account both the internal and external validity of the data, and should be tempered by considerations of cost and feasibility [18] (Table 4).

While for research purposes the quality domains include planning, design, data elements, data sources, ethics, privacy, and governance, for evidence the quality domains are described separately for registry participants, data elements, data sources, data quality assurance, analysis and reporting. As infrastructures that they are, registries are not research projects, and as for so many global concerns, there is no single funding source. However, it is highly recommendable that research questions should be answered by the data included (Table 4).
For registry developers, there is no established forum for sharing experiences. Therefore, each time a new registry is developed, it often starts from scratch (6, 10). Information on best informatics practices and common data templates would go a long way toward reducing the start-up costs associated with developing a registry. Some data elements might be common to all rare diseases (eg., sociodemographics, diagnosis, genetics, growth, medications, services), which raises the possibility of creating a core dataset that can be incorporated into all rare-disease registries.

A single individual, group, or even country will not lead the movement toward formation of a global rare-disease registry. As in the open-source software community, an open-science community for rare diseases is needed. Such a community would ensure that the conditions necessary for data exchange are addressed by defining common datasets, data standards, and vocabularies, and would provide a forum for exchange of experiences and knowledge. The biggest hurdle of a global registry is not technical, but rather the cultural obstacles to collaboration and data sharing across academic institutions and international boundaries.

5. Practical hurdles in establishing a database for rare diseases

Overcoming these hurdles is extremely important. A global infrastructure for a rare-disease registry will favour further orphan-drug legislation. Such a registry will draw new interest in rare diseases from academic researchers and the drug industry, since it will enable the design of more effective clinical trials and effectiveness studies, and the recruitment of patients much faster and at much lower cost.

A significant quantity of work is involved to gain ethical approval in all EU member states; approvals may be by country or by centre. Post marketing evaluation is interpreted, in some countries, as a phase IV with its specific requirements. It may be necessary to re-consent patients (i.e., if during the course of the database new objectives with other third parties get involved). There may be off label use of a drug (i.e., ketokonazole in the treatment of Cushing’s syndrome).

Funding sources and sustainability are a real issue; European registries initially funded have to find alternative means to subsist. On the other hand, industry registries may have unsustainable high costs and changes in upper management of a firm may underestimate the value of such registries and stop funding. Collaboration between academics and industry makes sense; but post-marketing commitments are for a much longer period than current funding of disease registries. Thus, it is worth considering worst case scenarios when industry and academic partners plan for long-term existence of databases.

6. The example of the European Registry of Cushing’s syndrome (ERCUSYN)

Cushing’s syndrome is a rare endocrine disease due to chronic exposure to hypercortisolism, both exogenous and endogenous. The diagnosis is often delayed and untreated Cushing’s syndrome has 50 % five year mortality, but “successful” control of hypercortisolism reduces, but does not eliminate, the long term morbidity. Recently persistent central obesity, cardiovascular risk, abnormal body composition and impaired quality of life have been shown to persist for more than 10 years despite remission of hypercortisolism. The perception of an unmet need in the diagnosis and management of patients with Cushing’s syndrome formed the basis of an application to the EC under the Public Health Program in 2006, the aims of which are described in Table 5. In comparison to product registries that include patients who have been exposed to biopharmaceutical products or medical devices, and health services registries consisting of patients who have had a common procedure, clinical encounter, or hospitalization, ERCUSYN is a disease or condition registry.

Since its initial set-up in 2007, it was decided that the ERCUSYN data and database should be owned by the European Society of Endocrinology (ESE), that is in fact an associated partner. It was funded by the European Commission for 3 years (2007-2010). Patient entry into the registry opened Sept 2008 and a webpage (www.ercusyn.eu) was constructed by the founding partners with specialist assistance from Lohmann&Birkner GMBH (Berlin), who were also an associated partner of ERCUSYN.

The ERCUSYN webpage offers brochures for patients and primary care physicians in different languages. It also contains a map with details on the currently 50 participating centres in 28 European countries which patients may use to identify centres of excellence. ERCUSYN has thus effectively formed a network among European centres of excellence in pituitary/adrenal endocrinology, which now can serve and function as terminals or web-nodes to recruit further endocrine centres from their respective European countries.

After an initial feasibility pilot study, the database permits patients diagnosed since 2008 to be entered prospectively or retrospectively in cases diagnosed since 2005 if an annual update can be provided. In October 2010 an initial analysis included data on 509 patients, of which 481 had a complete dataset. Data definitions are included in a detailed guidelines document available on-line and accessible from the database. Ethical and legal considerations guided the development and use of the ERCUSYN registry, respecting individual requirements in each participating centre or country.

After presenting data at the European Congress of Endocrinology (Rotterdam, May 2011), a publication has followed [19,20]. Some of the achievements and highlights reported include the following:

Table 5

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<tr>
<th>Initial aims of the European Registry of Cushing’s syndrome (ERCUSYN).</th>
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<tr>
<td>Improve the care and outcomes of Cushing’s syndrome in Europe</td>
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<tr>
<td>Identify the reasons for the delay in diagnosis, and establish optimal, cost-effective diagnostic investigation and therapy (surgery, radiotherapy, medical treatment) and define end points of treatment (biochemistry and quality of life)</td>
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<tr>
<td>Better appreciation of the long term impact on mental health and quality of life</td>
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<tr>
<td>Analysis of the regional differences in management with a view to disseminating best practice</td>
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• there is a long delay between onset of symptoms and diagnosis (2.9 ± 3.7 years; range 0–22, median 2 years);
• mean age at diagnosis is 44 ± 14 years, with a female predominance, as expected (390 females vs. 91 males);
• the ERCUSYN project allows an analysis of the heterogeneous clinical presentation. When patients were divided into 4 major etiologic groups: pitiary adenoma Cushing’s syndrome (CS) (PIT) (66 %), adrenal-dependent CS (ADR) (27 %), CS from an ectopic source (ECT) (5 %) and CS from other etiologies (OTH) (2 %), several differences were seen; i.e., in ECT males are more prevalent compared to the other groups (46 % vs 14–20 %, p < 0.01). The ADR group was significantly older than the PIT group (46.9 ± 13.6 vs. 42.7 ± 13.5, p < 0.05). ECT patients had a higher baseline prevalence of hirsutism compared to the global values (92 % vs 60 %) and diabetes (74 % vs. 38 %). Skin alterations (78 %), menstrual irregularities (63 %) and hirsutism (63 %) were more prevalent in PIT than in ADR (p < 0.01). When both sexes were compared, reduced libido was more prevalent in men (60 % vs. 40 %; p < 0.01), as well as vertebral osteoporosis (40 % vs. 20 %; p < 0.05), and vertebral (52 % vs. 18 %; p < 0.001) and rib fractures (34 % vs. 23 %; p < 0.05);
• initial symptoms often determined the specialist first consulted, which often missed the correct underlying diagnosis: ECT patients more frequently initially consulted a diabetologist, while gynecologists were consulted for initial complaints of CS more by women with PIT-CS or ADR-CS than with ECT-CS group (p < 0.05). Overall, weight gain resulted significantly more common in women than men (p < 0.01);
• baseline Quality of Life (QoL) evaluated by generic (EuroQoL) and disease-generated (CushingQoL) questionnaires were available in 27 % of the patients, and disclosed significantly lower scores of Visual Analogue Score (VAS) of the EuroQoL. (when compared to reference values from France and Spain), as well as significantly impaired QoL judged by CushingQoL.

7. Conclusion

The ERCUSYN project has begun to generate useful data answering some questions for which it was created; it demonstrates a heterogeneous clinical presentation of CS at a European level, depending on gender and etiology. The results presented above illustrate differences in clinical presentation depending on gender and etiology, confirms a long delay between onset of symptoms and diagnosis of CS, with a high number of specialists consulted who often missed the correct diagnosis. Furthermore, morbidity at diagnosis is high, with low bone mass, especially in men, and impaired QoL. Less than half the cohort was actively working, which is surprising in a cohort of patients with a mean age of 44 yrs. Thus, there is great potential for improvements in the time to diagnosis which would have obvious consequences for patients and for the health care systems that must meet the long term sequellae of delayed diagnosis.

Currently, ERCUSYN represents the largest collaboration of endocrine centres in Europe and has potential not only for improving the care of patients with Cushing’s syndrome, but also to extend its collaboration into new areas. It potentially may be used as a rare disease registry for an orphan drug to be evaluated, such as the new somatostatin analogue, Pasireotide. Thus, an academic registry set up before marketing authorization of the new drug as a disease registry may be liaised to the EMA-regulated, industry-required post-marketing surveillance study, to follow safety and efficacy in the long term outcomes in clinical practice conditions. Through the ESE this network may be used to disseminate information and encourage further interaction between endocrinologists across Europe.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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