The importance of translation of registries information into real-life practice on pulmonary arterial hypertension

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While randomized controlled trials (RCTs) remain the standard for evaluating the safety and efficacy of new drugs, the structured design of clinical trials is not always adequate for evaluating a range of other scientific objectives. The reasons why RCTs failed to give comprehensive information about pulmonary hypertension are linked to their well known defects: too brief trials, too few and simple ones, too median-aged patients. For these reasons there was a great development of a number of registries in the last 20 years which have enhanced the knowledge of the epidemiology, presentation, natural history, and pathophysiology of pulmonary arterial hypertension (PAH). Observational studies, when consecutive enrolment is employed, do not suffer from the selection bias that exists in almost all clinical trials, allowing for a more accurate and generalizable assessment of demographics, comorbidities and disease severity. Additionally, observational studies often have larger sample sizes and longer follow-up than clinical trials, such that long-term survival curves and prognostic factors can be evaluated and in-depth analyses may be pursued in subgroups of special interest. The absence of assigned treatment choices also provides greater opportunity to include patients who may not meet the standard criteria for a disease, patients for whom little is known about characteristics and outcomes.

Projects and registries like the Italian registry IPHNET (1) could give to the community that part of insights and precious indications on how better manage PAH patient's healthcare.

Up today, one of the main drawbacks related to the creation of registries lies in the approach used to deal with the patients who were enrolled well into their disease (prevalent subjects) in contrast to those who entered the study at the time of initial diagnosis (incident subjects).

Another methodological issue raised by registries involves the definition used to classify patients as 'incident'. For instance, in the French study (2), incident cases are those patients who received a diagnosis of PAH during the first year recruitment phase of the study. Conversely, in the REVEAL registry (3), incident cases are those patients who received a diagnosis of PAH within the 90 days prior to enrollment. This latter definition can introduce a time period during which no deaths could have occurred, known as 'immortal time'. These issues impact on the generalizability of the results, introducing or a survivor bias, which is a form of selection bias, or the immortal time bias. This may have led to an underestimation of mortality by both studies (REVEAL registry, French registry). A final issue relates to the

presence of confounding factors, due to the lack of selection criteria, and of missing values. Despite these known drawbacks, registry studies have provided estimation of the minimum (French study) and near maximum (Scottish study) incidence and prevalence of PAH. We now are aware that PAH prevalence - as calculated by registry studies - ranges between 15 and 50 patients per million inhabitants in Europe. Overall similar figures have been also reported in later registry studies. Registry studies have also investigated survival in PAH patients.

Registries also provided the basis for investigating PAH phenotype, using comparative analysis of different countries and time, they suggested that much of the phenotype changes were independent from the disease but were related to factors such as the healthcare environment, increased awareness of PAH by clinicians, changes in classification, easier access to medical information, and widespread use of noninvasive diagnostic techniques.

Similar results were obtained by analyzing data from a US observational study, although some differences between the REVEAL patients and US subjects with PAH were disclosed.

Collectively, the bulk of evidence derived until now from PAH registries demonstrates the potential of this tool for the evaluation of new treatment strategies and predictive markers of PAH in a real-life setting, even though the introduction of other PAH groups and larger entry criteria are envisaged to enrich the possible outcomes.

The Italian registry called iPHnet (Italian Pulmonary Hypertension Network) presents various characteristics such as facilitated access, data sharing and interoperability, update, patient's anonymity and data integrity. The system also enables the creation of patients' electronic health records (EHRs), the exportation and personalization of data and the possibility to design clinical report forms (CRFs) and collect information usable in clinical trials. In addition, it is possible to analyze the information present in the registry, creating graphs or other immediately available charts to evaluate the trends of a specific data and perform therapeutic or clinic adjustments. Treatment of data in the iPHnet database complies with FDA requirements, backup and disaster recovery policies and patients' privacy.

iPHnet is a flexible tool that integrates the capabilities of an EHR for PAH patients with those of a PAH registry. The ability to retrieve relevant information - although with all the limitations of any registry-based analysis - and to create appropriate CRFs will facilitate the development of prospective and retrospective trials aimed at providing new 'real-life' evidence on PAH.

In fact, this registry differs from others, since it works as an electronic chart for everyday clinical activity, with the possibility to extract focused data, and the FDA compliant certification allows the use of this data for clinical trials. Moreover the possibility of plotting the time course of clinical parameters, effort capacity, plasma biomarkers and hemodynamic parameters allows the identification of inadequate therapeutic response or clinical worsening.

Already planned projects with the iPHnet registry include, but are not limited to, a Clinical Worsening Calculator, the identification of novel biomarkers, a REVEAL risk score calculator, and the possibility of sharing information on patients for medical consultancies between centers. Real life data will help clinicians from non expert centres to standardize the PAH approach with expert centres, to ensure that every patient, independently from his geographical location, can receive the best solution for PAH, still an unresolved, devastating disease.

The iPHnet Project, a database used to collect health records on patients with PAH, can also be used for research purposes to retrieve *ad hoc* information. This network will serve as a tool for diagnostic and therapeutic appropriateness helping physicians and patients, but also giving effectiveness data of potentially great scientific interest.

References

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