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### **HEADING: DRUG AND ORPHAN DISEASES**

# **The challenges of pharmacoepidemiology of orphan drugs in rare diseases**

Rare diseases and pharmacoepidemiology

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## **Summary**

Large electronic health records database available at a national level offer great opportunity for research in rare diseases and orphan drugs. Methods and data used in pharmacoepidemiology present a great potential for epidemiology, drug utilization studies, drug safety, drug effectiveness and pharmacoconomics. This review presents the different sources of data in Europe, with a special focus on the French situation, with the recent implementation of SNDS (*systeme national des donnees de santé* [French national health data warehouse]). Some examples are given. Development of rigorous and innovative methods must be encouraged in the future.

## **KEYWORDS**

Rare disease, Orphan drug; Pharmacoepidemiology; Pharmacovigilance; Electronic health records

## **Abbreviations**

DDD: defined daily doses

EHRs: electronic health records

EU: European Union

FAERs: Food and Drug Administration adverse event database

FDA: Food and Drug Administration

GCA: giant cell arteritis

IMI2: innovative medicines initiative

IMiDs: immunomodulatory imide drugs

INSERM: French Institute for Medical Research (*Institut national de la santé et de la recherche médicale*)

ITP: immune thrombocytopenia

LTD: long term disease

NRDR: national rare diseases register

SNDS: French national health data warehouse (*système national des données de santé*)

SNIIRAM: French national inter regime health insurance information system (*système national d'information inter régime de l'Assurance maladie*)

WHO: World Health Organisation

## Introduction

Any disease affecting fewer than 5 people in 10,000 in the European Union (EU) is considered rare [1]. Although this might appear small, it translates into approximately 246,000 people at the European level. Most patients suffer from even rarer diseases affecting 1 person in 100,000 or more. Approximately 5,000-8,000 distinct rare diseases affect 6-8% of the EU population i.e. between 27 and 36 million people. The majority of rare diseases are of genetic origin, and are often chronic and life-threatening.

Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people [2-4]. It is a growing discipline that applies epidemiological techniques to study drug use in a large population. It could seem bizarre to apply the definition to rare diseases, since pharmacoepidemiology is intended to investigate the use and effects of medications on large populations. However, with the extension of large electronic health records database in a growing number of countries, covering large populations in number, exhaustiveness and long term follow-up, the input of pharmacoepidemiology in the field of rare diseases appears crucial.

## Definition of an orphan drug

An orphan drug is a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance. The conditions are referred to as orphan diseases. According to Orphanet [5], orphan drugs are intended to treat diseases so rare that sponsors are reluctant to develop them under usual marketing conditions. The process from the discovery of a new molecule to its marketing is long (10 years in average), expensive (several tens of millions of euros) and very uncertain (among ten molecules tested, only one may have a therapeutic effect). Developing a drug intended to treat a rare disease does not allow the recovery of the capital invested for its research. In this context, orphan drugs may be considered as drugs that are not developed by the pharmaceutical industry for economic reasons but

which respond to public health need. An updated list of orphan drugs available in Europe is available on Orphanet [5].

### **Benefit-risk assessment of orphan drugs**

In the case of rare diseases, marketing authorization for orphan drugs may be given with limited data regarding efficacy and safety. Exhaustive data collection in the context of real life for patients treated with orphan drugs is particularly relevant as it allows the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorization is usually granted at a time when evidence is still limited although already somewhat convincing.

Classically, this exhaustive information comes from specific registries implemented at a local, national, European or international level. Patient registries and databases encourage the development of clinical research in the field of rare diseases, as well as improve patient care, and healthcare planning. No uniform standards govern the collection, organisation, or availability of this data. More than one registry often exists for the same rare disease, while existing registries account for approximately only 20% of all rare diseases. The European Commission is therefore advocating for the creation of a European Platform on Rare Diseases Registration that would act as the focal point for rare diseases registries in the EU.

A limited but increasing number of orphan drugs are reaching patients. However, the majority of rare diseases are still without any effective treatment. EU funded projects strengthen the links between academia and industry to translate research results into new diagnostic tools and therapies. Innovative medicines initiative (IMI2) supports projects accelerating the research and development process for drugs for rare diseases. Research on rare diseases is also important since rare diseases can serve as models for more common diseases and the complexity of rare diseases often requires multidisciplinary innovative approaches.

## Panel of existing rare disease registries in Europe

A recent report by Orphanet published in May 2019 provides a complete list of the 600 rare diseases registries in Europe. This report gathers the information collected by Orphanet so far, regarding systematic collections of data for a specific disease or a group of diseases. The report includes data about EU countries and other countries participating to the Orphanet network. The diseases or groups of diseases covered by each register are provided with their Orpha number which is the unique identifier in the Orphanet nomenclature. For France, the data collection has been supervised by the French Institute for Medical Research (*Institut national de la santé et de la recherche médicale* [INSERM]). Among the complete list, 143 disease registries are identified in France: 19 have a regional coverage, 103 national, and 11 and 6 have respectively a European or a universal coverage. These registries identified in France cover different diseases and populations. For example, among them, 5 correspond to congenital malformation registries located in specific French geographic area and contribute to EUROCAT network, and 17 to specific cancer registries located in limited areas. The national rare disease database (*banque nationale de données maladies rares* [BNDMR]) is also present in this complete list (see below).

Specialized registries are centralised in a unique database on rare diseases at a national level in two European countries: Italy (*registro nazionale malattie rare*) [6] and Spain (Spanish rare diseases registries research network, Spain-RDR) [7]. These national registries provide a unique portal for health professionals and patients to participate in data collection about drug utilization, health care pathways and studies investigating effectiveness and safety. Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients.

## The French context

In France, the BNDMR is a priority project of the second wave of the national plan for rare diseases supported by the Ministry of Health [1]. The low number of subjects, the low coverage in terms of population and the limitations related to actual health data sources do not allow to ensure high quality population-based studies in the context of rare diseases. The implementation of a collection of data specific to rare diseases through the BNDMR aims to improve this field of research [8].

This national database aims to provide France with a homogeneous collection of data based on a minimum data set to document the management and health status of patients with rare diseases in French expert centers, and to better evaluate the effect of national plans. One of the objectives of this national database is to allow the linkage between clinical registries or cohorts of patients with rare diseases in France with exhaustive reimbursement data covered by the French national health data system (*système national des données de santé* [SNDS]), including hospitalization and ambulatory care pathways at a national level. This record linkage would provide knowledges on the health economics point of view, and would allow to implement national studies for a better assessment of the prevalence rates of rare diseases and of the effectiveness of orphan drugs after their initial approval in the context of real life. The agenda of the spreading of this database can be consulted on [9].

The recent and encouraged access to the French SNDS is an opportunity to develop researches on the topic of rare diseases and orphan drugs, because the exhaustiveness of the data, and the coverage of these drugs by the French health insurance system. Interests and limitations of these databases are well described in a recent review [10].

## Some examples of pharmacoepidemiological approach in the field of rare diseases.

Some recent reviews highlight the potential interest of pharmacoepidemiological approach for research on orphan drugs in rare diseases, but much remains to be done in this domain. Crisafulli et al [11] discussed challenges regarding real-world data sources related to rare diseases in Italy. The minimum common dataset for the Italian national rare diseases register (NRDR) is similar to that of the BNDMR. Actually, at the end of 2014, the Italian NRDR contained information on 200,000 patients, but the completeness and accuracy of the data present some shortcomings. There are 2 other types of data sources potentially relevant to the monitoring of drug use among patients with rare diseases: Italian claims databases (often available for whole cities and regions) and electronic health records (EHRs) databases which can provide much useful clinical information on both rare diseases and orphan drug use, although their potential in these fields has been not completely explored. The linkage of orphan disease registers with claims or EHRs has much potential to improve orphan drug surveillance. The authors expect improvement by enrichment with these data, but for the moment in Italy, it seems to be limited. Italy claims database have been widely explored for drug safety purposes, but not to study orphan drugs. Trifiro et al [12] underlined these challenges for drug utilization researches, implementation and impact of risk minimization measures, drug safety and comparative effectiveness. Some examples can be found for paediatric pharmacology, which is often at the frontier of orphan diseases [13,14].

## **Drug utilisation studies**

Stolk et al [15] performed a pilot study to determine, for drugs used in an outpatient setting, how utilisation of centrally authorised drugs varies across a selection of EU member states, in particular focusing on drugs that have received an orphan medicine status. Among the orphan drugs authorised between 2000 and 2006 in EU, they selected five drugs available in the ambulatory setting: imatinib mesilate (Glivec<sup>®</sup>), bosentan (Tracleer<sup>®</sup>), zinc acetate dihydrate (Wilzin<sup>®</sup>), nitisinone (Orfadin<sup>®</sup>) and sodium oxybate (Xyrem<sup>®</sup>). The study was performed in 6 European countries: Austria, Denmark, Finland, Portugal, The Netherlands, and Sweden, and estimated drug utilisation rates as a measure of uptake in the health system. Utilisation rates were expressed as the number of defined daily doses (DDD) per 1000 inhabitants per year. They estimated “between-

country variability in use” by calculating the relative standard deviation (RSD) for the utilisation rates of individual drugs across countries. This measure for variability in use was calculated as follows:

$$100 * \frac{\text{Standard deviation of utilization as DDDs/1000 persons/year across countries}}{\text{Average of utilization as DDDs/1000 persons/year across countries}}$$

Taking in account the utilisation rates of other centrally authorised non-orphan drugs, the study showed that drugs with an orphan medicine status were, in general, more expensive and had a higher innovation score than drugs without an orphan medicine status. The analysis did not find any association between variability in use and orphan medicine status. The authors concluded that the variability in use of orphan medicines in the different health care systems of the European Union appears to be comparable to the other newly authorised drugs that were included in the analysis. This analysis was performed at a macroscopic level, but showed the feasibility of this approach.

Palmaro et al described cancer drug regimens focusing on the use of immunomodulatory imide drugs (IMiDs) and patterns of drug utilization to prevent thromboembolism in the context of real life for patients with multiple myeloma by using SNDS data [16,17]. A similar approach has been done to investigate the recommended vaccination rate in a population of patients with immune thrombocytopenia [18].

## **Rare diseases epidemiology**

Poujois et al [19] estimated the prevalence of Wilson disease (WD) in France in 2013 through the French national inter regime health insurance information system (*systeme national d'information inter regime de l'Assurance maladie* [SNIIRAM]), by combining information of hospital database, reimbursed drugs and long term disease (LTD) status. They identified all patients in 2013 with a LTD with ICD-10 code E83.0 for copper metabolism disorders. Second, they used the 2011, 2012 and 2013 hospital discharge diagnoses to identify all individuals discharged from hospital at least

once with a principal, related or associated diagnosis ICD-10 code E83.0 for copper metabolism disorder or the “Orphanet” WD code (MR905) over this three-year period. Third, they applied a composite definition according to which patients were considered to have WD when they complied with either the first or second definition. Information regarding comorbidities was obtained using other associated LTD diagnoses. WD drug therapies were defined by at least one reimbursement in 2013 for D-penicillamine or zinc acetate, as well as antidepressant medications. The composite definition (LTD and hospital diagnoses) identified 906 prevalent cases, yielding a crude prevalence of 1.5 cases per 100,000; 1.65 per 100,000 in males and 1.44 per 100,000 in females. The authors also investigated the care pathway of these patients during the year 2013. Finally, this study underlines the contribution of administrative data to provide information on Wilson disease in France. This information can enrich and facilitate case detection for specific disease registries.

Moulis [20,21] et al used the same approach to identify and estimate at a nationwide level the epidemiology of immune thrombocytopenia (ITP) by using a validated definition algorithm [22]. Incident ITP patients were identified among patients with hospitalization and/or LTD attribution for ITP, with ICD-10 code D69.3. Several steps with exclusion criteria (erroneous codes after the first diagnosis), persistence with treatments by ITP drugs (systemic steroids, thrombopoietin receptor agonists ...) were applied to determine incident cases [22]. Overall ITP incidence was 2.92/100 000 person-years (95% CI: 2.83-3.01). It was higher in females (3.03/100 000 person-years, 95% CI: 2.90-3.16) than in males (2.77/100 000 person-years, 95% CI: 2.64-2.90). The incidence was 2.83/100 000 person-years in those <18 years of age (95% CI: 2.63-3.00) and 2.94/100 000 person-years in adults (95% CI: 2.84-3.05). A peak was observed in children aged 1 to 5 years, with the highest incidence in younger boys. A second peak was observed in adults >60 years of age, reaching 9/100 000 person-years (95% CI: 8.21-9.95) in men >75 years of age.

In a recent review about the input of electronic health care databases in the field of oncology, Conte et al [23] highlighted the value of nationwide health insurance databases such as the French SNDS to identify specifically rare onco-haematological diseases. To better identify rare hematologic diseases such as multiple myeloma or lymphoma, validation procedure for identification algorithms have been published [24,25]. In the case of Hodgkin lymphoma, the identification algorithm presented high performances (sensitivity of 95% and predictive positive value of 74%) which opens the opportunity of investigating care pathways in this very rare disease.

Using these algorithms gives the opportunity to characterize at a nationwide level the prevalence and/or incidence rate of a specific rare disease in a more accurate way.

Another example concerns the epidemiology of type 1 diabetes in France [26]. Actually, some types of type 1 diabetes are defined as rare disease [27]. A recent study investigated the incidence of type 1 diabetes in children France based on data from the SNDS for the period 2010-2015 [28]. The authors present a specific algorithm in 2 steps, with a first selection of any code of type 1 diabetes and insulin prescription in children between 6 months and 14 years old, and a second step of exclusion of children with iatrogenic diabetes or related with another chronic disease. With this approach, they estimated an annual incidence rate, which increased by 4% between 2010 and 2015 (from 15.4/100,000 to 19.1/100,000 100 000 person-years), in both gender and age groups.

## **Pharmacovigilance studies**

Although the regulatory framework for pharmacovigilance does not differentiate orphan drugs, those orphan drugs that have been approved in recent years present unique challenges for pharmacovigilance departments. The limited size of a study population for an orphan indication, sometimes only a few dozen or 100 patients, results in a small adverse event dataset at the time of drug approval. Moreover, in the context of rare diseases, clinical trials are often uncontrolled or comparative data might have been collected from a historical control group. Therefore, the safety profile remains poorly known at the time of approval [11,12,29-31].

Some new generation of orphan drugs target diseases which were always lethal diseases in the young and create a new population of survivors who have a course of disease never previously seen. Therefore, a new adverse reaction detected as the underlying rare disease progresses while the patient grows could be the consequence of the disease rather than an adverse drug reaction to the orphan drug [32].

Conventionally, for drugs administered to hundreds of thousands, or millions, of patients, a signal of a possible safety hazard arising from a single case report would be first evaluated by scrutinizing large national or international pharmacovigilance databases, such as the Food and Drug Administration (FDA) adverse events database (FAERs), Eudravigilance for the EU, or Vigibase<sup>®</sup>, the World Health Organisation (WHO) pharmacovigilance database, as well as review of evidence from clinical trial data. Confronting the number of reports of a given event to drug exposure data enables calculation of a reporting rate, which can be related to comparator drugs (the principle of the prescription event monitoring system), or to occurrence of the event among untreated patients [33]. However for an orphan drug, the maximum expected number of patients in North America and European Union together may be lower than some thousands, with a low probability to detect a sufficient number of cases. Data coming from drug registries are insufficient in size, with failure in exhaustiveness and follow-up. To improve the quality of post approval safety assessment [34], disproportionality analysis on large pharmacovigilance database is possible and beneficial, even if examples remain rare [35,36]. A disproportionality analysis in the WHO pharmacovigilance database (Vigibase<sup>®</sup>) has shown of a signal for an increased risk of thrombosis with eltrombopag compared with romiplostim, whereas these 2 drugs are both thrombopoietin receptor agonists approved in the treatment of immune thrombocytopenia [37].

## **Drug effectiveness studies**

Clinical pharmacology presents a vital role in accelerating orphan drug development and overcoming some of these challenges [38]. Large electronic health records databases used in pharmacoepidemiology (combined or not with specific clinical data collected in rare disease registries) may facilitate recruitment of patients for clinical trials or implement pragmatic trials [39]. They could also be used in the context of research hypothesis or for establishing the “proof of concept” with existent drugs potentially of interest in another context of rare disease. In the real-life settings, these approaches can also incorporate a comparator (alternative drug or other therapies) which is often missing in pre-approval studies. It can be a way to verify the global effectiveness of the orphan drug.

## Pharmacoeconomics

Data used in pharmacoepidemiology and particularly those coming from claims databases are by definition completely accurate for a pharmacoeconomics' point of view. A study performed on the SNDS at a regional level has described the economic burden of the giant cell arteritis (GCA) [40]. A specific analysis study investigating direct costs related to the management of patients with GCA showed that when polymyalgia rheumatic (PMR) was associated with GCA, the economic burden of the disease was higher by 75% compared to GCA patients without PMR. These additional costs were driven by a higher probability of hospitalization, even after adjusting on cardiovascular comorbidities [41]. To the best of our knowledge, these studies were the first in France giving information related to the economic burden of this rare disease at the population level. Other aspects of pharmacoeconomics in the field of rare diseases concern generic drugs. The very high cost of orphan drugs is a highly debated issue and a cause of limited access to treatment for many patients. Generics are important components of measures introduced by healthcare regulatory authorities to reduce treatment costs. In most patients and conditions the switch from a branded drug to its generic counterpart is performed with no major complications. However, evidence from complex diseases suggests that generic substitution requires careful evaluation in some settings and that current bioequivalence criteria may not always be adequate for establishing the interchangeability of branded and generic products [42]. This is particularly accurate in the field of rare diseases. This complexity may be aggravated by the specific context of biosimilar drugs, which could have a considerable impact on the economic burden of rare diseases [43]. In a recent study on the economic impact of antiretroviral generics in Europe (which are not really devoted to a "rare disease"), we found that the overall savings observed in real-life from generic antiretroviral drugs were more related to brand price-reduction than to high rate of low-price generic utilization [44].

## Conclusion

This panorama highlights the potential of pharmacoepidemiology and its methods in rare diseases and orphan drugs, for epidemiology, drug utilization studies, drug safety, drug effectiveness and pharmacoconomics. Rigorous and innovative methods must be encouraged in the future. Access to the data of the French SNDS is an opportunity to improve the scientific knowledge in this field.

### **Disclosure of interest**

The author does not report any conflict of interest related to this topic.

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