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Pharmacoepidemiology Studies: what Levels of Evidence and how can They be Reached?

Maryse Lapeyre-Mestre[1], Claudine Sapède[2], Nicholas Moore[3] and participants of round table N° 5 of Giens Workshops XXVIII: Pascal Bilbault[4], Patrick Blin[5], Damien Chopy[6], David Evans[7], François Gueyffier[8], Laure Lacoin[9], Muriel Malbezin[10], Joëlle Micallef[11], Dana Morlet-Vigier[12], Sophie Muller[13], Emmanuel Oger[14], Yannick Plétan[15], Gérard Pons[16], Patrice Verpillat[17] and Caroline Vigneau[18] †

1 Service de Pharmacologie médicale et clinique, Université de Toulouse, INSERM 1027, Toulouse, France
2 Affaires économiques, Laboratoire Roche, Boulogne, France
3 Service hospitalo-universitaire de Pharmacologie, Université de Bordeaux, INSERM U657, Bordeaux, France
4 Laboratoires Boehringer Ingelheim, Reims, France
5 Université de Bordeaux, Bordeaux, France
6 Inserm Transfert, Paris, France
7 Laboratoires Lilly, Suresnes, France
8 Université Lyon 1, Hospices civils de Lyon, Lyon, France
9 Haute Autorité de Santé, Saint-Denis la Plaine, France
10 Laboratoires Janssen, Issy-les-Moulineaux, France
11 CIC-UPCET, Hôpital la Timone, Marseille, France
12 IMS Health, Puteaux, France
13 Laboratoires GlaxoSmithKline, Marly-le-Roi, France
14 Université de Rennes 1, Rennes, France
15 Laboratoires Roche, Boulogne-Billancourt, France
16 Université Paris Descartes, Assistance Publique – Hôpitaux de Paris, Paris, France
17 Laboratoires Lundbeck, Issy-les-Moulineaux, France
18 Centre Hospitalier Universitaire, Nantes, France

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Abstract – In pharmacoepidemiology studies, the nature of the research question will dictate the choice of methodological approach and the conditions for optimizing the level of evidence. Thus, to document the treated population and the modes of use of a new drug in real-life prescribing conditions, a descriptive approach through cross-sectional or longitudinal studies conducted on databases, or else ad-hoc studies, will be preferred. On the other hand, evaluation of the real-life "effectiveness" of a new drug will be based on cohort, case-control or scientific modeling, depending on the drug and the disease of interest. For questions involving drug risks and safety, it is the adverse effects profile that will guide the choice of study design, both for identification of the effect (signal) and assessment of causation. In all cases, in the post-marketing authorization (MA) setting, the evidence acquired in pre-MA studies serves as the basis for generating hypotheses. Whatever the research question and the method chosen to address it, the potential biases and their impact on the results need to be identified. In certain cases, a combination of several complementary approaches may prove preferable to a single study.

Abbreviations: see end of article.

† Articles, analyzes and proposals from the Giens workshops are those of the authors and do not prejudice the position of their parent organization.

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Fig. 1. Comparison between hierarchies of studies according to their confidence value (level of evidence) for example as defined by Bradford Hill causation criteria[5] and *Haute autorité de santé*.[6]

1. Introduction

Pharmacoepidemiology studies and, more generally, studies evaluating the impact of drugs, have been the subject of numerous manuals, publications and guidelines. Over the last 10 years, this theme has been debated at the round tables of the Giens workshops. In 2002, round table No. 2 addressed the post-marketing evaluation of drugs and described the different possible methodologies as a function of the questions asked.[1] In 2004, round table No. 2 examined the respective roles of comparative clinical trials and cohort monitoring studies in the pre- and post-marketing assessment of drugs.[2] The 2010 workshops (round table No. 5) debated the role of post-marketing studies from a standpoint of risk assessment and pharmacovigilance.[3] In 2011, the impact of drugs in the real-life setting was analyzed through scientific modelling approaches.[4]

In 2012, the topic of pharmacoepidemiology studies was addressed, in terms of levels of evidence and how they can be reached. To propose a pragmatic approach, the working group decided to examine the subject from the perspective of the question being asked (usually by health authorities or institutions), since this constitutes the starting point for any reflection and therefore guides the choice of methodology. Furthermore, the nature of the question and possibly the time frames in which it must be answered define the conditions for optimizing the level of evidence (considerations of quality, biases and cost).

The questions were divided into three main categories:
- conditions of use/identification of target and treated populations;
- "effectiveness" or performance of the drug in real-life conditions of prescription and use;
- safety and risk assessment.

2. System approach

The working group reflected upon the best possible approach, according to the context of studies of use on the one hand, which aim to document the real-life conditions of use of a drug, or the context of association studies, pertaining either to effectiveness or safety, on the other. For each of these two domains, the working group discussed the most appropriate criteria by which to answer the question, ultimately based on the Bradford Hill guidelines for causation.[5]

Classically, studies are placed into hierarchies according to their confidence value underpinned by the design of the study itself (clinical trial, cohort or case-control study, etc.), and the general assumptions about potential biases. However, these hierarchies were developed primarily in a context of demonstrating efficacy and do not necessarily apply to other domains of post-marketing assessment (figure 1). For example, according to the French Health Authority (*Haute autorité de santé*, HAS) recommendations for elaborating clinical practice guidelines,[6] studies are classified into four levels of evidence, from level 1 (randomized clinical trials [RCT] with high power; meta-analyses) to level 4 (case series, retrospective studies). This leads to a ranking of recommendations from A (established scientific evidence conferred by data from level 1 studies) to C (low level of evidence, corresponding to low-quality retrospective studies or case series).

Other sources also propose categorizing the level of evidence according to study design, with the same hierarchy.

According to the Oxford Centre for Evidence Based Medicine (CEBM), the level of evidence of a study can be graded down due to intrinsic weaknesses, imprecision, indirect nature of evidence, inconsistency between studies, or an absolute effect size that is too small.[7] Independently of study design, the level of evidence can conversely be graded up if the effect size is large or very large. Also, according to the CEBM, the level of evidence of a systematic review is always higher than that of an individual study. The grading of recommendations assessment, development and evaluation (GRADE) recommendations for rating the quality of evidence[8] are based on study design (trials or observational studies) and propose five reasons to possibly rate down the quality of evidence (bias, inconsistency, indirectness, imprecision and publication bias) and three reasons to possibly rate up the quality of evidence (size of effect,