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Point of view

Randomized clinical trials and observational studies in the assessment of drug safety

Essais cliniques randomisés et études observationnelles dans l'évaluation de la sécurité des médicaments

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Abstract

Randomized clinical trials are considered as the preferred design to assess the potential causal relationships between drugs or other medical interventions and intended effects. For this reason, randomized clinical trials are generally the basis of development programs in the life cycle of drugs and the cornerstone of evidence-based medicine. Instead, randomized clinical trials are not the design of choice for the detection and assessment of rare, delayed and/or unexpected effects related to drug safety. Moreover, the highly homogeneous populations resulting from restrictive eligibility criteria make randomized clinical trials inappropriate to describe comprehensively the safety profile of drugs. In that context, observational studies have a key added value when evaluating the benefit-risk balance of the drugs. However, observational studies are more prone to bias than randomized clinical trials and they have to be designed, conducted and reported judiciously. In this article, we discuss the strengths and limitations of randomized clinical trials and of observational studies, more particularly regarding their contribution to the knowledge of medicines' safety profile. In addition, we present general recommendations for the sensible use of observational data.

Keywords: Epidemiological methods; Evidence-based medicine; Observational studies; Randomized controlled trials; Risk-benefit assessment

Résumé

Les essais cliniques randomisés sont considérés comme le modèle préféré pour évaluer les relations causales potentielles entre médicaments ou d'autres interventions médicales et les effets attendus. Pour cette raison, les essais cliniques randomisés sont généralement la base des programmes de développement dans le cycle de vie des médicaments et la pierre angulaire de la médecine fondée sur les preuves. Cependant, les essais cliniques randomisés ne constituent pas le modèle de choix pour la détection et l'évaluation des effets inattendus liés à la sécurité des médicaments. De plus, les populations très homogènes résultant de critères d'éligibilité restrictifs rendent les essais cliniques randomisés inappropriés pour décrire de façon exhaustive le profil de sécurité des médicaments. Dans ce contexte, les études observationnelles ont une valeur ajoutée majeure lors de l'évaluation du rapport bénéfice-risque des médicaments. Cependant, les études observationnelles sont plus sujettes aux biais que les essais cliniques randomisés et elles doivent être conçues, menées et rapportées très judicieusement. Dans cet article, nous discutons les points forts et les limites des essais cliniques randomisés et des études observationnelles, plus particulièrement eu égard à leur contribution à la connaissance du profil de sécurité des médicaments. En outre, nous exposons des recommandations pour une utilisation rationnelle des données observationnelles.

Mots clés : Méthodes épidémiologiques ; Médecine fondée sur les preuves ; Études observationnelles ; Essais cliniques randomisés ; Bénéfice-risque

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1. Introduction

In the modern era, the slow rise towards a rational clinical medicine has been built around two pillars: the progressive integration of the basic sciences in clinical practice and the rise of clinical epidemiology [1,2]. In the beginning of the 20th century, the Flexner report [3] recommended the integration of basic sciences in medical schools' core curriculum. Eighty years later, a beautiful series of articles discussing a new vision for teaching clinical medicine enabled the rise of clinical epidemiology. The first of these papers [4] launched the evidence-based medicine era in clinical medicine, which emphasized the importance of the epidemiological method in the assessment of causal evidence.

Around the end of the 19th century and the beginning of the 20th, pharmaceutical industry–sometimes in close contact with academic researchers [5] – developed powerful ''magic bullets'': antiserum against diphtheria toxin, arsphenamine (the first partially effective treatment for syphilis) [6] and insulin [7]. Physicians and researchers in clinical research, preoccupied with the assessment of efficacy of their treatments developed progressively sophisticated methods [8], until coming up the current ''gold standard'', the randomized clinical trial (RCT).

Although, it seems today quite natural to say that rational prescribing in the context of contemporary medical sciences supposes the identification of a biological path between the drug and its observed effects as well as a control of the clinical efficacy through RCTs, but it was not always quite as evident [9,10].

Throughout drug history, and from a drug safety perspective, it was only after a series of disasters, that pharmacovigilance came into being [11]. For instance, the St Louis incident (diphtheria anti-toxin serum contaminated by tetanus) [12] and a disaster that occurred in 1937 from the use of diethylene glycol as a solvent for sulfanilamide [13], did not result in any change in industry practice. The change eventually occurred only after the notorious case of thalidomide that upset the international community in 1961 [14].

In response to the thalidomide disaster, the World Health Organization (WHO) established its programme for International Drug Monitoring promoting in this way pharmacovigilance. The WHO defines pharmacovigilance as ''the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem''.

Two recent examples highlight the need to continue advances in pharmacovigilance. In 2004, five years after its introduction on the US market and more than 20 million users, rofecoxib, a cox-2 inhibitor, doubled the risk of myocardial infarction and stroke [15]. Again, in 2014, France suffered from the benfluorex tragedy [16]. Although these drugs followed strict RCT guideline, they point to the need to strengthen the post-marketing surveillance, to monitor prevailing patterns of drug-use within the real-life setting [17].

Recently, the adoption of new Directive and Regulation by the European Parliament and Council of Ministers in December 2010 brings significant changes in the safety monitoring of medicines across the European Union. By enabling and promoting the conduct of post-authorization safety studies (PASS), the European Union legislation strengthened the post-authorisation monitoring of medicines in Europe [18]. The main aims for conducting PASS are:

- the evaluation of safety concerns associated to marketed medicinal products;
- the description of the patterns of drug use, which may impact the safety profile of the drug, and;
- the evaluation of the effectiveness of risk management measures.

Specific objectives related to the evaluation of safety include the quantification of important risks, the assessment of risks associated with long-term use, the investigation of the potential risks in populations for which safety information is limited or missing (e.g. children, elderly, pregnant women) and the confirmation of the absence of particular risks of concern.

PASS are usually designed in the form of observational studies (OS) also referred as non-randomized or non-interventional studies [19]. However, OS play different roles and are conducted at different stages of the drug development. For example, incidence and prevalence studies are needed to describe the epidemiology and to assess the burden of the disease of interest. These studies could be conducted before a new medication is introduced into the market or even before the start of the clinical development programme. They may be important for estimating background risks in the population of interest, allowing sensible comparisons with the observed risks after the introduction of new drugs into the market [20]. In addition, OS designed for signal refinement can be implemented in active surveillance programmes during the post-authorisation phase. OS studies may be also needed for assessing the effectiveness of marketed drugs in real-practice settings. In this paper, the main focus is on OS performed in the post-authorisation phase for the assessment of potential adverse drug reactions (ADRs) of interest. Other usual pharmacovigilance activities like individual case reviews and disproportionality analyses of spontaneous reports are not discussed.

This opinion paper aims at reviewing the limitations of the RCTs and contributing to the discussion about the role of the OS in the assessment of the safety profile of drugs.

2. RCTs: strengths and weaknesses

When looking at evidence strength through the hierarchy of evidence, RCTs are more regarded than OS, because of the methods RCTs usually employ to handle potential biases [21–23]. Randomization and allocation concealment bypass the possibility of a selection bias and theoretically warrant a balanced distribution of confounders between the compared groups [24,25]. Blinding, when it is applicable, allows to control for several potential sources of information bias (at the level of the patient, the investigator, the care provider and/or the

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