MGR BARTOMIEJ OCHYRA

„The role of medical literature in signal detection”

STRESZCZENIE W JĘZYKU ANGIELSKIM

The aim of the pharmacovigilance system is identification of new risks related to the use of medicinal products. The goal of the system is also detection of qualitative and quantitative changes in known risks (e.g., increased risk frequency, increased symptoms severity, unusual course of an adverse drug reaction (ADR) etc.). The characterization of risks is based on signal detection and signal assessment. Signal detection includes both statistical analysis and manual review of individual case safety reports (ICSRs – hereafter as ‘report’) and the associated clinical evaluation. One of the key sources of information for signal detection is medical literature.

According to Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 a ‘signal’ means information arising from one, or multiple sources, including observations and experiments, which suggests a new, potentially causal association, or a new aspect of a known association between an intervention and an event, or set of related events, either adverse or beneficial, which is judged to be of sufficient likelihood to justify verificatory action.

In order to increase signal detection, a Marketing Authorisation Holder (MAH), i.e., the pharmaceutical company, has to perform medical literature monitoring through the review of medical databases (e.g., MEDLINE, Embase or Excerpta Medica) at least once a week, and monitoring of local, non-indexed medical journals in countries where their medicinal products have a marketing authorization (hereafter as ‘local journals’).

The purpose of this doctoral dissertation was to evaluate the efficiency of medical literature monitoring and the impact of literature reports on signal detection. The main goal of the research was achieved through the following specific objectives:

1. Assessment what is the literature reports contribution to the process of signal detection for signals which led to changes in the summary of product characteristics (SmPC) (so called product-information update) in terms of ADRs and/or warnings associated with the use of a medicinal product.
2. Analysis of information on ADRs published in Polish medical journals.
3. Comparison of search in MEDLINE and Embase versus manual full-text review of medical journals in order to retrieve information on ADRs.

The first objective was verified by analyzing data from the EudraVigilance (EV) database. Data for all drug-event association (DEA) for which the European Medicines Agency (EMA) performed a signal assessment between January 2016 and September 2018 that led to a SmPC update were analysed. The change in SmPC update had to include: a new ADR or a new ADR frequency or new special warnings and precautions for use. In total, 4,160 reports which led to SmPC update of 73 different DEAs were assessed. Approximately 33% of these reports originated from the medical literature. In total, 1,206 (88.42%) literature reports were created based on medical journals indexed in MEDLINE or Embase or EBSCO (IPA/AMED). Most reports were created based on medical journals indexed in Embase.

The second objective was verified by analyzing data retrieved during a manual full-text review of 84 medical journals published in Poland between January 2018 and December 2019 for 1,142 active substances (drugs). Eighty-four journals published in Poland were selected for review based on the medical journal selection recommended by the Polish Society of Pharmacovigilance (PSPharm). The type of information on drug adverse events or reaction published in Polish medical literature and the parameters characterizing the journal, which may indicate the usefulness of the journal in the process of signal detection and signal assessment were assessed. A total of 4,867 pieces of safety information were identified, of which 1,650 (33.90%) were adverse events (AEs), 886 (18.20%) ADRs, 258 (5.30%) serious adverse events (SAEs), 163 (3.53%) serious adverse drug reactions (SADRs) and 269 (5.33%) drug interactions – the rest of the safety information was classified as special situations (33.74%), of which the most frequently reported was lack of efficacy (1.340; 27.53%). Over 48% of safety information was identified in 10 of the 84 medical journals, where 3 of them had journal Impact Factor (IF), 6 of them were indexed in the MEDLINE and/or Embase, and 5 of them had an affiliation to a scientific society. A correlation was found between journal Impact Factor and the amount and type of safety information, and correlation between number of SAEs and journal indexation in scientific databases (MEDLINE and/or Embase).

To achieve the third goal, 20 active substances (drugs) were randomly selected for polish medical literature review and search of their ADRs in the next step has been performed. The studied period covers three years from January 2018 to December 2020 and 1,576 reviewed individual journal issues with 20,146 articles. A search for literature reports for selected drugs during manual full text review of journals was performed and then compared to the outcome of the database search in MEDLINE and Embase.

After exclusion of reports originating from review articles, reprints and cited sources - 66 literature reports were retrieved. Thirty reports (45.45%) originated from journals indexed in

bibliographic databases (MEDLINE or Embase). Three out of 20 (15.00%) reports originating from journals indexed in MEDLINE and 9 out of 30 (30.00%) reports published in journals indexed in Embase were not found during analysis of this databases. Three reports from MEDLINE and 3 reports from Embase were created based on conference abstracts. Moreover 6 reports from Embase originated from journal supplements. One (5.88%) report in MEDLINE and 3 (14.29%) reports in Embase would have been retrieved during database search if the search strategy used the drug name alone. Moreover, 5 (29.41%) reports in MEDLINE and 2 (9.52%) reports in Embase would not have been retrieved even if the search strategy used the drug name alone. Database entry date was, on average, 119 days later than article publication date.

The following conclusions can be drawn from the research: Approximately one-third of the data used to signal assessment that result in SmPC update comes from medical literature, with over 88% of these literature reports were prepared based on journals indexed in medical databases. In polish medical journals the majority of ADRs description is published in polish language only, which makes them inaccessible for indexation in the medical literature databases. The effectiveness of search for literature reports is better using manual, full-text review of journals than a search in medical databases. During a search in medical database there is risk of missing up to 30% of reports presented in journal supplements or at conferences, and up to 30% of reports, due to improper drug indexing or defective search strategy.