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Pharmacovigilance of biosimilars and other biologicals within the hospital: current practices and future challenges

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In the coming decade, many patents for biological pharmaceuticals will expire. Consequently, the market for biosimilars has the potential to grow rapidly. For safety reasons, the more extensive use of a greater variety of biologicals increases the importance of adequate traceability of each administered product and batch. In essence, accurate pharmacovigilance and post-marketing surveillance are needed. This paper summarizes the associated challenges faced by hospitals, and their role in the current and future pharmacovigilance of biosimilars and other biologicals. Recent experience at the Ghent University Hospital in Belgium is described to provide an example of the contribution hospitals can make to the improved pharmacovigilance of biologicals.

Keywords: Biologicals, biosimilars, hospitals, pharmacovigilance

Many patents for biological medicinal products will expire over the coming decade, and the market for biosimilars has the potential to grow rapidly. As the number and quantities of biologicals being used in patients increases, so does the importance of adequate traceability of each administered product and batch. Accurate pharmacovigilance (PV) systems within hospitals are required. This paper summarizes the challenges faced by hospitals in the current and upcoming environment, and their role in the PV of biologicals including many biosimilars.

Biosimilar skepticism: a role for pharmacovigilance

PV is an important issue for biologicals, including biosimilars. It is a legal requirement for all biologicals: European PV legislation (EU No. 520/2012) provided several obligations, which were followed by the good pharmacovigilance practice guidelines released by the European Medicines Agency [1, 2].

However, skepticism about biosimilars results from substantial differences in the required non-clinical and clinical data between a biosimilar and an innovative biological product. Whereas phase III clinical trials are the main focus in the development of a biological originator, to demonstrate a positive risk–benefit balance, the off-patent evidence gathered in biosimilar development is dominated by physicochemical and functional characterization and pharmacokinetic studies, with the purpose of demonstrating comparability. For this reason, the adoption of a biosimilar in a given country is influenced by the reservations of decision-makers, reimbursement authorities, prescribers, pharmacists and patients. Moreover, the extrapolation of clinical data between indications based on sensitive endpoints, and the rapidness with which biosimilars are being developed might promote concerns about clinical efficacy and safety. These barriers need to be addressed carefully because biosimilars offer an improved access to treatments for cancer, diabetes, arthritis and other important diseases globally.

In fact, the comparability approach has been used for decades in biotechnology-derived pharmaceutical production: numerous changes have been made in manufacturing processes while maintaining safety and efficacy [3]. Public awareness of these dynamic production changes has increased recently, in parallel with biosimilar development. Thus, the acceptance of a biosimilar goes hand in hand with its ability not only to demonstrate effectiveness, but also to demonstrate a similar safety profile to the originator. The collection of comparable safety data for the biosimilar as for the originator via an accurate PV process would support broader acceptance. Good PV will consolidate the available objective information, which is in turn one of the strategies to overcome barriers to uptake [4].

The effectiveness and value of pharmacovigilance

In the event of a safety issue, a good traceability process – within hospitals for example – should make it possible to find unused batches and to identify patients treated with the affected biological. The periodic safety update report (PSUR) should be updated, and referral to a benefit–risk reassessment is a plausible outcome.

However, some important remarks can be made regarding the value of current PV processes. The extent to which important safety problems for biologicals have been reported through PSUR updates in the European Union has thus far been rather small compared with the total number of PSUR updates performed. Benefit–risk reassessment procedures have resulted in positive outcomes in the majority of cases [5]. PV monitoring activities resulting from PSUR assessment have rarely led to label

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changes. Moreover, Bouvy et al. studied the value of these PV activities in relation to their ability to promote better health care and found that they were not cost-effective, a finding that was partially due to the very small number of important safety issues discovered (two issues between 1995–2009) [6]. This finding of cost-ineffectiveness illustrates the need to find an optimum balance between the intensity of PV activities and other measures such as improving access to tackle urgent healthcare needs.

It is further noteworthy that the conclusions of PV processes largely depend on the quality of information that feeds into the system (sufficient and accurate), so that real signals can be distinguished from noise and appropriate responses can be made. Biologicals are often used as second- or third-line therapies in patients with other concomitant therapies and different prognostic profiles. Channelling bias of databases – due to prescription of drugs in a more diverse population than previously studied – can easily occur, making analysis and detection more complex.

Pharmacovigilance in hospitals: a Belgian case

This section describes efforts to install an optimal, voluntary PV reporting system at the Ghent University Hospital in Belgium. Throughout Europe, many biologicals are currently used in hospitals or day clinics embedded in the hospital structure. Thus, some PV information should be captured in these hospitals. Many hospitals have spontaneous reporting systems. Adverse drug events, preventable or not, are collected and analysed by quality teams (in many cases consisting of quality coordinators, physicians, pharmacists and nurses). Adverse events with clinical consequence should then be transferred to national authorities [7].

This is also the case at the Ghent University Hospital, a 1,000-bed tertiary care hospital. An electronic reporting system has been set up for non-preventable events, which involves the upload of information related to the event, such as drug, dose, dilution fluids, administration time and concomitant (pre)medication, from electronic hospital systems, such as computerized physician order entries and other recording systems in oncology, among others. Currently, our hospital is not equipped with a scanning system to record brand name and batch number during drug administration. Consequently, batch information is often not readily available and recording this information needs in most cases cooperation with the pharmacy department. Sometimes this can lead to the designation of more than one batch, taking into account the several batches circulating in the hospital within the relevant time frame. Brand names, on the other hand, can be traced in the pharmacy system through the delivered products. Only in the case of pharmacy preparation is the batch information always available, since batch numbers and brand names are then recorded for every preparation given to a patient (to comply with good manufacturing practice). These observations are consistent with the findings of Klein et al. [8], who reported more successful brand name detection (76%) as compared with batch number knowledge (5%) in voluntary hospital reporting.

Recognizing the importance of accurate PV reports, we have recently implemented an updated PV plan that contains the following actions:

1. Since 2014, we have had an in-hospital dedicated point of contact (POC) for 'active PV', enabling timely analysis of every incoming report of a non-preventable adverse drug reaction (ADR). POC is a hospital pharmacist who is a member of the hospital quality team and the Pharmacy and Therapeutics Committee.
2. POC ensures communication of these ADRs with the national authorities [7] and company registries.
3. Since 2009, an online reporting system (Iprova™, Infoland, The Netherlands) has automatically generated email traffic to different analysts such as POC. This has diminished the amount of missing information. Follow-up actions can be designated in both directions between reporter and analysts. In 2016, the pharmacy policy was to start ADR analysis within two working days.
4. Since 2016, the online system for reporting ADRs has been separated from that for other in-hospital incidents such as falls and medication errors. A separated system was needed because of the specific nature of the ADR reports. A new platform will be released in 2017 to enable switching between the systems: if one starts to enter data in the other-incidents system, one can then switch to the ADR system and continue to input data with minimal effort. Currently, the ratio of other medication incidents to ADRs is 100:1.
5. In the ADR reporting system, a causality algorithm (based upon the Naranjo probability scale) was added to enable a first evaluation of the relationship between the drug and the adverse event.
6. For confidentiality reasons, spontaneous reports lose their link with patient identification at the moment a report in the other-incidents system is electronically closed. This formerly led to incomplete information if it was later decided that the incident was an ADR. The new ADR reporting system is a secured environment wherein the link with patient identification remains assessable under appropriate conditions, even after internal closure of the report.

The challenges in future pharmacovigilance analysis

Because of the specific nature of spontaneous ADR reports (under-reporting), they cannot be considered separately from PV information collected in drug- and disease-based registries. The post-marketing information collected in these registries should be aggregated with voluntarily reported and suspected ADRs. This is also needed to identify rare side effects, such as progressive multifocal leukoencephalopathy [9].

From a practical point of view, the registration of batch information (next to brand name) before leaving the pharmacy or at the moment of administration is technically possible, but requires many manual steps. Bar code scanning would be a major improvement, provided that every single unit has a batch-encrypted code, since hospitals work with a unit-dose distribution system. The latter is strongly encouraged by the European Association of Hospital Pharmacists' statement and policy

documents [10]. Other efficiency gains exemplified in the Danish national action plan could also be beneficial, such as automatic data transmission from local electronic health record systems to the national authority [11]. Vermeer et al. recently summarized the traceability of biologicals in clinical practice and discussed this in light of the expected changes in supply chain standards and the challenges of electronic exchange of exposure data [12].

Further attention should be paid to the fact that biosimilars are not only distributed by hospitals, for example, the upcoming market of the biosimilar insulins. In Belgium, community pharmacies scan the overall package which is a positive element. The organization of registries and collection of clinical data on the other hand can be more challenging in a community pharmacy setting.

Lastly, to address risks related to the handling of monoclonal antibodies (mAbs), our hospital recently developed a risk assessment model and flow chart to evaluate the potential risks of manipulation of mAbs. Safe handling recommendations are based on the risks of immunogenicity and toxicity of the biological involved. Unsafe handling of a biological can lead to altered immunogenicity, and hence effectiveness. The recommendations were established using a risk matrix and with regard to operational and clinical considerations [13]. This policy allows the preparation and handling of mAbs (either biosimilars or originators) to be undertaken in the central pharmacy or on the ward. Stratification by risk class will contribute to more accurate PV information for these biologicals with a high risk–benefit.

For patients

Hospitals should record the brand names and batch numbers of all biological drugs used in patients, including biosimilars. Accurate information for a specific drug is required in case adverse effects occur. This process is increasingly computerized, but some challenges still remain. Potential improvements include the use of bar code scanning each time a drug is administered to a patient, in order to have all correct information available in the electronic patient record.

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References

1. European Commission. The rules governing medicinal products in the European Union – Guidelines on pharmacovigilance for medicinal products for human use – Volume 9B [homepage on the Internet]. [cited 2017 Feb 8]. Available from: https://ec.europa.eu/health/human-use/pharmacovigilance_en
2. European Medicines Agency. Guidelines on good pharmacovigilance practices (GVP). EMA/529641/2016. 15 August 2016 [homepage on the Internet]. [cited 2017 Feb 8]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/08/WC500211731.pdf
3. Vezér B, Buzás Z, Sebeszta M, Zrubka Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016;32(5):829-34. doi:10.1185/03007995.2016.1145579. Epub 2016 Feb 25.
4. Moorkens E, Jonker-Exler C, Huys I, Declerck P, Simoens S, Vulto AG. Overcoming barriers to the market access of biosimilars in the European Union: the case of biosimilar monoclonal antibodies. Front Pharmacol. 2016;7:193.
5. Bouvy JC, Huinink L, De Bruin ML. Benefit-risk reassessment of medicines: a retrospective analysis of all safety-related referral procedures in Europe during 2001–2012. Pharmacoepidemiol Drug Saf. 2016;25(9):1004-14.
6. Bouvy JC, Ebbers HC, Schellekens H, Koopmanschap MA. The cost-effectiveness of periodic safety update reports for biologicals in Europe. Clin Pharmacol Ther. 2013;93(5):433-42.
7. Federal Agency for Medicinal and Health Products [homepage on the Internet]. [cited 2017 Feb 8]. Available from: https://www.fagg-afmps.be/en/human_use/medicines/medicines/pharmacovigilance
8. Klein K, Scholl JH, Vermeer NS, et al. Traceability of biologics in The Netherlands: an analysis of Information-Recording Systems in clinical practice and spontaneous. Drug Saf. 2016;39(2):185-92.
9. Giezen TJ, Straus SMJM. Pharmacovigilance of biosimilars: challenges and possible solutions. Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4):118-9. doi:10.5639/gabij.2012.0103-4.033
10. European Association of Hospital Pharmacists. Bar coding medicines to the single unit [homepage on the Internet]. [cited 2017 Feb 8]. Available from: http://www.eahp.eu/practice-and-policy/bar-coding-medicines-to-the-single-unit
11. Lunddahl B. Pharmacovigilance on biologicals and biosimilars: a Danish perspective. Generics and Biosimilars Initiative Journal (GaBI Journal). 2016;5(3);123-4. doi:10.5639/gabij.2016.0503.030
12. Vermeer NS, Spierings I, Mantel-Teeuwisse AK, et al. Traceability of biologicals: present challenges in pharmacovigilance. Expert Opin Drug Saf. 2015;14(1):63-72.
13. Alexander M, King J, Bajel A, et al. Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. Intern Med J. 2014;44(10):1018-26.

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