Riassunti delle relazioni finali dei progetti di ricerca svolti dagli studenti nell'ambito del tirocinio formativo del master per l'anno accademico 2019-2020

Relocation of the local pharmacovigilance responsibilities to an affiliate: challenges and operating procedures

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ABSTRACT

Introduction: Since the first international program was implemented, the importance of pharmacovigilance has been emphasized. A pharmacovigilance centre is necessary in every country and the process of creation is long and it requires knowledge and governmental support. Some steps have been described, focusing on the process known as "capacity building", which can be applied to the pharmacovigilance network, and the responsibilities of the Marketing Authorization Holders.

Objective: To describe the transfer of the local pharmacovigilance duties from the headquarter to a new affiliate, highlighting the operational steps that have been carried out.

Methods: Following the creation of the new legal entity, the local pharmacovigilance unit of the Italian headquarter company started to prepare the transfer of responsibilities in both practical and procedural terms, by organizing bi-weekly meetings which were focused on the activities and the arisen problems.

Results: An intercompany Safety Data Exchange Agreement (SDEA) was drawn up between the headquarter and the newborn affiliate to define how the Parties have to cooperate in order to comply with its respective pharmacovigilance obligations. The above document was also used as reference to describe procedures and responsibilities for the management of any pharmacovigilance activity performed. A new local contact point for pharmacovigilance (LCCP) was also appointed and registered in the Italian pharmacovigilance network.

Conclusion: Most of the activities needed for the transfer of the responsibilities, have been put in place in respect of the planned timelines.

Keywords: Pharmacovigilance Centre, Marketing Authorization Holder, Pharmacovigilance Responsibilities, Transfer, Affiliate.

Post-marketing safety of a medical device containing high- and low-molecular weight hyaluronans: insights from a 5-year experience

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ABSTRACT

Background: Since the development of minimally invasive procedures, the use of dermal fillers has significantly increased and revolutionized the approach to cosmetic surgery. Hyaluronic acid (HA) dermal fillers are widely used because of their hygroscopic properties, biocompatibility and reversibility. Preparations of HA containing both high and low molecular weight HA are known as hybrid cooperative complexes, which seem to have better performance in both cosmetic and regenerative medicine. Profhilo® is a class III medical device based on stable cooperative hybrid complexes developed thanks to NAHYCO® hybrid technology and is indicated for facial treatments.

Aim: Post-marketing safety data are important to complete the product information of Profhilo®. Therefore, our aim was to review post-marketing safety data of Profhilo® obtained after the first 5 years of marketing, updating the initial review carried out after 3 years of marketing.

Methods: Safety data were collected annually through global spontaneous reports covering a five-year period (February 2015-February 2020). Safety data were evaluated in relation with global sales data. Assuming that the highest number of syringes that can be used by a patient for a 1-year cycle is 7, the number of the exposed patient was estimated as the number of sold syringes divided by 7.

Results: The number of patients exposed to Profhilo® almost doubled every year and the estimated number of exposed patients was 200,508 until February 2020, whereas the previous 3-year report included only 42,394 subjects. Overall, a total number of 37 adverse events were reported in the global database. Only one event was considered clinically significant and reported as incident. The most frequently observed reactions were early-onset reactions at injection site such as swelling, oedema, redness, ecchymosis, and erythema. Less frequent late-onset local reactions (e.g., swelling, nodules) were also observed. Causality assessment both by the reporting physician and IBSA concluded that they were local reactions due to hypersensitivity and/or to inappropriate injection techniques. All events resolved without any significant complication according to treatment guidelines.

Conclusions: Although underreporting of minor events cannot be ruled out, the overall number of reports is very low, especially if we consider the total exposure. This supports the overall safety of the product.

Keywords: Medical Device, Safety, Aesthetic Medicine, Hyaluronic Acid.

Biological drugs during treatment for IBD in pregnancy: a disproportionality analysis of Food and Drug Administration Adverse Event Reporting System (FAERS) database

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ABSTRACT

Objective: The aim of this study was to investigate signals of disproportionate reporting (SDRs) of clinical relevance related to the use of biological drugs during pregnancy approved for Inflammatory Bowel Diseases (IBD).

Methods: All suspected adverse events (AEs) related to maternal/foetal outcomes registered in the FDA Adverse Event Reporting System between January 2000 and June 2020 were collected. The reporting odds ratio (ROR) was used as a measure of disproportionality to identify possible SDRs related to biologics.

Results: A total of 50,299 ICSRs involving pregnant women were identified from FAERS, 997 reports concerning IBD patients. From the total cohort (N=997), were retrieved 15 (1.5%) reports related to *neonatal disorders,* 16 (1.6%) to *foetal disorders*, 180 (18.1%) to *labour and delivery complications*, and 291 (29.2%) to *termination of pregnancy and risk of abortion*. For each cluster of AEs, ROR has been performed. According to the crude ROR and 95% CI, biological drugs (infliximab, adalimumab, golimumab, certolizumab, vedolizumab, and ustekinumab) did not present any SDRs for all these clusters of AEs, with ROR<1, confirming their safety during pregnancy. Moreover, a significant ROR<1 has been observed for Certolizumab Pegol and *"termination of pregnancy and risk of abortion"* [ROR 0.39 (0.17-0.88)], which could be interpreted as a potential reduced risk.

Conclusions: In this study the potential safety issues associated with the use of biologics during pregnancy for IBD patients was investigated. Findings from this analysis confirmed the favourable benefit/risk ratio of biologics in this context. Further detailed analyses are still necessary to better investigate these associations.

Keywords: Pharmacovigilance, Pregnancy, FAERS, IBD, Safety.

Cardiac safety evaluation of azithromycin, lopinavir-ritonavir and remdesivir used for the treatment of COVID-19: a European Pharmacovigilance Study

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ABSTRACT

Background: The novel Coronavirus disease (COVID-19) outbreak represents the greatest medical challenge in decades. COVID-19 affects multiple organs, including the cardiovascular (CV) system. Arrhythmia, cardiac injury fulminant myocarditis, heart failure, pulmonary embolism and disseminated intravascular coagulation (DIC) are the most common cardiovascular complications associated with COVID-19. The lack of drugs specifically approved for the treatment of COVID-19 has led to the use of repurposed existing drugs, such as azithromycin, lopinavir/ritonavir and remdesivir. While azithromycin and lopinavir/ritonavir are known to be associated with cardiac risks, little is known about remdesivir cardiotoxicity. Furthermore, pre-existing morbidities, particularly CV diseases, increase the severity of COVID-19.

Objective: To collect and provide preliminary assessment of safety data on cardiotoxicity of azithromycin, lopinavir/ritonavir and remdesivir in COVID-19 patients.

Methods: We investigated the European pharmacovigilance database (Eudravigilance, EV) and downloaded all Individual Case Safety Reports (ICSRs) containing at least one suspected drug among azithromycin, lopinavir/ritonavir or remdesivir. All of the collected ICSRs were received between January 1st to November 11th, 2020. We then selected only the ICSRs which included at least one cardiac adverse event and in which the therapeutic indication of our suspected drugs was "COVID-19" or a similar term.

Results: 276 ICSRs were retrieved from EV, of which, 145 ICSRs were related to remdesivir, 65 to azithromycin, 38 to lopinavir/ritonavir, 25 to the association azithromycin and lopinavir/ritonavir, and 3 to the association azithromycin and remdesivir. The median age of patients was 65 years. Most of the ICSRs were observed in male patients and were reported by Healthcare Professionals rather than by Non Healthcare Professionals. 269 out of 276 ICSRs were classified as serious. Azithromycin most reported cardiac adverse event was "Electrocardiogram QT prolonged" (18), while lopinavir/ritonavir and remdesivir most reported cardiac adverse events were "Sinus bradycardia" (12) and "Cardiac arrest" (48) respectively. The most reported outcome was "fatal" (105).

Conclusions: Given the potential seriousness of induced cardiac adverse drug reactions and considering the intrinsic methodological limitations of our study as well as the recent use of these medicines for the treatment of COVID-19, we believe that further clinical studies should be conducted on this topic to better estimate the impact of these therapies on cardiac safety in COVID-19 patients.

Keywords: Cardiotoxicity, COVID-19, Azithromycin, Lopinavir/Ritonavir, Remdesivir.

Management and assessment of the risk profile of biological products in pharmacovigilance

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ABSTRACT

Background: Biological medicines are a rapidly growing area of interest to many large and small pharmaceutical companies. A biological medicinal product contains an active substance that is produced by or extracted from a biological source. Biologicals are high-risk products, due to their complex nature and their potential for variability of quality, safety and efficacy, as consequences of changes in the manufacturing process. Another key feature of these products is their potential immunogenicity that could result in adverse drug reactions (ADRs) and/or lack of efficacy cases. The European Medicines Agency (EMA) has released a guideline describing how to monitor the safety profile of biological medicines and how to build a proper risk management strategy to guarantee a favourable benefit-risk balance over time.

Objective: To describe how a Marketing Authorization Holder (MAH) can manage and characterize the risk profile of biological products, with the purpose of optimizing and ensuring a favourable benefit-risk balance.

We analysed the entire pharmacovigilance reporting process, from the first reporter to the pharmaceutical company, and we identified criticalities that may impact the management of biological products. We also discussed possible approaches to be implemented at MAH level.

Results: Our analyses showed that the main criticalities related to biological products are: lack and/or poor quality of data collected in case reports, showing that the missing information are exactly those needed for an accurate causality assessment; limitations of the spontaneous reporting system, with particular difficulties for MAHs in charge of assessing the incidence of ADRs; differences among classes of biological drugs resulted in substantial differences also in the occurrence of immunogenicity related ADRs; difficulties for MAHs in complying with all the Good Vigilance Practice (GVP) requirements; issues in obtaining drug utilization data from healthcare databases (e.g. patients registers); issues in the batch-specific analyses in signal detection; manufactural changes that could have significant impact on the efficacy and safety of the final product; lack of communication between pharmacovigilance and all the stakeholders involved in the management process.

Conclusion: Given the great variability of biological products, we can affirm that the risk assessment and management of biological products must be product-specific, tailored to the product, in order to ensure a favourable benefit-risk profile.

Keywords: Biological Medicines, Adverse Drug Reaction, Marketing Authorization Holder, Benefit-Risk Profile, Risk Management.

Safety of adalimumab-biosimilar drugs following therapeutic switch from originator

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ABSTRACT

Introduction: Adalimumab is a fully human anti-tumour necrosis factor monoclonal antibody, indicated for the treatment of multiple inflammatory disorders, including rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. The launch of adalimumab biosimilars introduced the possibility of switching between originator medicine and its biosimilars.

Aim: To analyse adverse drug reactions (ADRs) following therapeutic switch from adalimumab reference product (RP) to its biosimilars; to identify studies on RP-biosimilar switching in scientific literature; to analyse adalimumab biosimilars reports in the US Food and Drug Administration Adverse Event Reporting System (US FAERS).

Methods: We collected and analysed ADRs reports in patients switched from adalimumab RP to its biosimilars. Secondly, we performed a systematic literature search in PubMed database to identify studies on RP-biosimilar switching. Lastly, we investigated the US FAERS records between the fourth quarter of 2018 and the fourth quarter of 2020. Adalimumab case reports, focusing on biosimilar products, were selected and analysed.

Results: 175 patients switched from adalimumab RP to its biosimilars (83.3%), and ADRs occurred in 17.1% of cases. The most reported Preferred Terms were 'Arthralgia' (12.7%), 'Psoriasis' (11.1%) and 'Injection site reaction' (7.9%). Phase III clinical trials on switching from adalimumab originator to biosimilars did not reveal efficacy or safety profile variations. In real-life studies, the switch from adalimumab originator to biosimilars was associated with adverse events and lower drug efficacy, with subsequent switch-back to the originator product. In the US FAERS, the most represented Preferred Terms for case reports describing both originator and biosimilar products were 'Product substitution issues' (6.1%), 'Drug ineffective' (2.5%) and 'Injection site pain' (2,5%).

Conclusions: From the available data, it is not clear whether the switch from originator can lead to increased adverse events or loss of therapeutic effect. This is a topic worthy of further investigation, due to the short period since marketing authorisation of adalimumab biosimilar drugs, and the lack of real-life studies about switching.

Keywords: Adalimumab, Biosimilars, Switch, ADR.

The new medical devices regulation UE 2017/745 (MDR): towards a new successful operational company mindset

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ABSTRACT

Background: In May 2021 the New Regulation (EU) 2017/745 MDR will be introduced together with the commissioning of EUDAMED, the first European Databank on Medical Devices. These changes will require compliance with new requirements. Our aim was to analyse the obligations regarding the surveillance system for clinical investigations according to MDR, studying in deep how promoter/investigator should behave in pre-market clinical investigations and post market clinical follow-up (PMCF). Another aim was to discuss the method of reporting and managing device deficiency and incidents through the analysis of specific case studies on medical devices. The final objective purpose was to outline the basis for the review and creation of new corporate Standard Operating Procedures and "working instructions".

Methods: We considered all available sources: Italian legislation, Standard ISO 14155: 2020 Third Edition, MEDDEV and Medical Device Coordination Group guidelines, essential to outline the new legal framework in the field of Medical Devices and to consolidate knowledge of current standards. Two case studies, one pre- and one post-market, were used to define how to operationally manage the reporting of adverse events: who must report, what should be reported and to whom, and the timelines in pre-market and post-market clinical investigations. An active exchange with the Italian Ministero della Salute, General Directorate of Medical Devices and Pharmaceutical Service Office VI - Clinical Trials made it possible to carefully analyse every possible scenario.

Results: Starting from the analysis of the two clinical studies mentioned above, an active exchange with the Ministero della Salute bring to understand each vigilance report in detail. The role of all actors involved in the reports of serious adverse events (expected or not), device deficiency (malfunctions), and incidents related to the use of medical equipment and devices was highlighted. As highlighted through the discussion, the New MDR 2017/745 regulation reflects the need to move towards a more careful and concrete regulation in the context of medical devices, with the main objective of increasing the health and safety protection of patients and users, reducing the likelihood that the same type of harmful incident will occur several times thereafter.

Conclusions: New Regulation (EU) 2017/745 MDR will aim to ensure the proper functioning of the internal market for medical devices, based on a high level of protection of the health of patients and users. This will involve the need to create specific Standard Operating Procedures and "working instructions" through working groups specialized in the management of the most relevant issues in the field of medical devices. An increase in the traceability of the device throughout its life and an increase in the control of technical documentation will have a significant impact on quality standards contributing to the creation and to the continuous updating of a solid Quality Management System. The real effects of the application of the MDR can only be measured after a reasonable period of time and only in the near future we could have an effective assessment of the efforts made by all the actors involved in the sector.

Keywords: Medical Device, MDR 2017/745, Device Deficiency, Incident, Serious Adverse Events (SAE, SADE, USADE, ASADE).

Signal validation: review of a case analysis with focus on data integration through EVDAS tool

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ABSTRACT

Background: The EudraVigilance data analysis system (EVDAS) is a tool developed to provide safety relevant information from EudraVigilance (EV). Although EVDAS has been available for Marketing Authorisation Holders (MAHs) since November 2017, at present we are still in a trial period and MAHs, whose medicinal products are not on the "pilot list", do not have any obligation to use EVDAS in their safety monitoring activities. Still, this obligation will soon be extended to all products and, in any case, it is recommended that MAHs extend their safety monitoring activities using EVDAS.

Objectives: To gain experience with this tool and define its role in the signal management process and Individual Case Safety Reports (ICSRs) evaluation.

Methods: The analysis of a potential drug-event combination (DEC) between Ceftriaxone and Kounis Syndrome (KS) was performed. ICSRs were collected from the company database and from EV through EVDAS. A qualitative assessment (case by case analysis) was performed by the medical consultant. The assessment concerned the seriousness and expectedness of the ADR and its causality strength of relation to drug administration (through the WHO-UMC Causality Categories). After the qualitative assessment, a quantitative assessment was carried out through a disproportionality analysis using the disproportionality measure ROR (reporting odds ratio), defining a Signal of Disproportionate Reporting (SDR) when the 95% confidence interval lower bound of the ROR was > 1. Finally, a broader search in literature relative to KS was performed. Starting from the analysis of this sole previous experience we trace the path, with the purpose of extrapolating a simple working scheme and discuss how data retrieved through EVDAS can integrate our analysis.

Results: In the company database a total of 6 KS ICSRs related to ceftriaxone were retrieved from the company database. The ROR based on the company database did not show a clear Signal of Disproportionate Reporting (SDR) (ROR=2.68; [0.99;7.27]). Ten cases were retrieved through EVDAS. The Ceftriaxone-KS DEC was reported as having a SDR, as the 95% confidence interval lower bound of the ROR for the concerned DEC, using all the other DECs available in the database as reference, was 2.82.

Conclusion: Considering the collected data, the association between ceftriaxone administration and Kounis Syndrome could not be excluded. Because of the potential life-threatening course of KS, it was decided to keep this DEC monitored and to review the relevant data in the PV database, EVDAS, and literature at least on a yearly basis.

Keywords: EVDAS, Safety Monitoring, Signal Validation, Kounis Syndrome, Ceftriaxone.