

RIASSUNTI DELLE RELAZIONI FINALI DEI PROGETTI DI RICERCA SVOLTI DAGLI STUDENTI NELL'AMBITO DEL TIROCINIO FORMATIVO DEL MASTER PER L'ANNO ACCADEMICO 2015-2016

Disproportionality analysis of adverse cardiovascular reactions of macrolide and fluoroquinolone antibiotics based on the WHO spontaneous reporting database

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ABSTRACT

Introduction: Macrolides and fluoroquinolones are used worldwide since decades. However, new safety concerns arising from recent case reports and observational studies have suggested a possible association between the exposure to these drugs and the onset of cardiovascular adverse reactions. To date, results were sometimes conflicting. The aim of the present study is to provide the contribution of real-life data onto the ongoing discussion about cardiovascular toxicity of both macrolides and fluoroquinolones by a disproportionality analysis of data from Vigibase, the WHO database of spontaneous ADRs reporting.

Methods: Data were retrieved from Vigibase until 31st May 2016. Macrolides and fluoroquinolones were compared to amoxicillin, as a class and individual drugs, by using the Reporting Odds Ratio (ROR) (with 95% CIs and p value) to assess the strength of the potential drug-reaction association. Medical Dictionary for Regulatory Activities (MedDRA) was used to classify ADRs: only those belonging to the System Organ Class (SOC) 'cardiac disorders' and 'vascular disorders' were considered. Furthermore, it was verified whether the specific MedDRA_PT (Preferred Term) was acknowledged in the Summary of Product Characteristics (SPC) of the corresponding drug. Macrolides were then assessed versus fluoroquinolones to clarify which antibiotic class was more prone to causing cardiac ADRs.

Results: Six thousand eight hundred and ten reports were retrieved; 62% of them were serious and 35% concerned female. For both macrolides and fluoroquinolones, significant RORs for 'Atrial fibrillation' and 'Arrhythmia' versus amoxicillin were identified. In addition, some disorders of ventricle rhythm, such as *Torsades des pointes*, reached significance. Furthermore, macrolides showed a significant positive association to 'Bradycardia' and 'Cardiac arrest'. Analyzing macrolides versus fluoroquinolones, the former resulted more frequently associated with 'Atrial' or 'Ventricular fibrillation' than fluoroquinolones. Azithromycin, clarithromycin and levofloxacin were listed more frequently in association to cardiac ADRs, but also moxifloxacin and ciprofloxacin were often reported.

Conclusion: Beyond the limitations of the study method, these findings highlighted that macrolides and fluoroquinolones could influence cardiac rhythm and induce life-threatening diseases, particularly in patients with underlying cardiovascular risk factors. Although these ADRs seem to be not common, they have a notable impact on clinical practice because of the huge number of the exposed subjects.

Keywords: Macrolides, Fluoroquinolones, Pharmacovigilance, Cardiovascular safety, Disproportionality.

Off-label drugs in the cancer institute “Giovanni Paolo II” Bari: data analysis and the implementation of the procedure

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ABSTRACT

Background: Off-label refers to the use in clinical practice of drugs already registered, but differently prescribed by the provisions in the technical specifications approved by the Ministry of Health. It often concerns widely known molecules, but for which new scientific evidences suggest that they should be used even in clinical situations not covered by the technical specifications of the drug.

Objective: One of the clinical areas where off label drugs are most prevalently used is cancer. In particular, the most recurrent pathologic requests in oncological and haematological cancers have been taken into consideration to assess all the reasons for which off label anti cancers medicines are used in compliance with the current regulations and the clinical results of therapy performed on the patient. 85 cases of off-label requests (period 2011-2015) have been observed and two most recurrent oncological and haematological pathologies have been identified and an official authorization to examine the medical records of patients has been granted.

Results: Only in 33% of cases, there was an adequate informed consent to the patient. The results showed a great use of off label drugs; only in one case, the therapy could not prevent the patient death due to a highly aggressive and advanced malignancy. In all other cases, the treatment had positive effects on the prognosis and on the quality of life. The clinical area that gave the best results was the haematology: all patients with Hodgkin lymphoma treated in the last year with Brentuximabvedotin + Bendamustine obtained a complete remission of the disease.

Conclusions: The topic of off label use is still controversial in Italy: on the one hand it can promote the clinical trial creating valid therapeutic alternatives for patients, on the other It must be carefully controlled to prevent a disproportionate use that can have important complications both for the health and for the responsibility of the doctor and the Hospital.

Keywords: Off-label, Oncology, Hodgkin lymphoma, Small cell lung cancer, Patient-safety.

Consumption and off-label use of quetiapine in nursing homes in Ticino

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ABSTRACT

Background: In the last decades, atypical antipsychotics have been studied and developed for their characteristic to combine psychiatric disease treating and reduction of adverse reactions as extrapyramidal syndrome. Quetiapine is one of the most prescribed drug of this pharmacological class among elderly population. Inappropriate medication prescription is a common cause of preventable adverse drug events among elderly population where a number between one and two out of three older patients have an increased risk to receive a potentially inappropriate drug compared to general population.

Method: Collection of anonymous data from 15 nursing homes located in different zones of Ticino including: number of total residents, residents taking quetiapine, age, sex, quetiapine daily dosage, indication, prescribing doctors (general practitioner, specialist, hospital physician).

Results: In an elderly population mostly represented by 80-90-year-old residents in nursing homes, 75.1% of quetiapine prescriptions were made by general practitioners. Quetiapine was mostly prescribed for agitation (31.3%) and dementia (27.9%) which are off-label indications. As regards dosage, most of them were under 50 mg/die, much lower than the 200 mg-daily-dosage authorized by Swiss Agency for Therapeutic Products for diseases like schizophrenia or bipolar disorder.

Conclusions: Most of quetiapine prescription comes from general practitioner who tend to prescribe it at a lower dosage and off-label. Increasing the percentage of prescription by psychiatrists or geriatricians would probably lead to a more appropriate prescription of quetiapine.

Keywords: Quetiapine, Off-label, Appropriate prescription, Nursing home, Ticino.

Management and reporting of post-marketing adverse events to medicinal products: the US requirements and their differences with the European ones

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ABSTRACT

Background: To guarantee drug safety, regulatory authorities have been prescribing increasingly demanding and accurate pharmacovigilance (PV) activities for several years, and marketing authorization holders (MAHs) must comply with the PV legislations of all the countries in which their products are authorized. For multinational pharmaceutical companies, this could mean to deal with different PV systems having a duty to fulfill different requirements. To successfully address this issue, the personnel responsible for PV activities should be familiar with the single legislations and with similarities and differences among them.

Objectives: Here we analyse PV legislative references of US, providing a short description of the regulatory authority's organization, and of the postmarketing reporting requirements, comparing them with those in force in the European Union (EU).

Results: We found important analogies but also several differences between US and EU reporting requirements for Individual Case Safety Reports (ICSRs) and periodic reports related to postmarketing products. Moreover, analyzing the reports received during the last calendar year related to four generic medicinal products of which IBI Lorenzini SpA is the MAH, we found that the number of ICSRs which met the criteria to be reported individually and/or in periodic reports to FDA is quite different from that which should be reported to EMA.

Conclusions: Despite the effort to harmonize PV requirements, important differences between US and EU PV systems still persist, and whether these differences may affect drug safety evaluation remains an open question that will require complex studies to be addressed.

Keywords: Pharmacovigilance, FDA, reporting criteria, PADER, PSUR.

The new pharmacovigilance legislation: risk management plan as tool of safety in the context of Public Health.

Analysis of Risk Management Plan on Vardenafil for a Generic Application

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ABSTRACT

This report aims to present the drawing up and the Authority assessment process of the RMP for the application of a generic medicinal product. This work was born from the legislative duty of companies in developing a pharmacovigilance dynamic document about the safety of their medicinal products. This draft is a work of data collection and has been defined thorough a bibliographical research and by using the resources provided by the Applicant. It starts from the analysis of the last three-years European Commission Report, regarding the European Pharmacovigilance System activities, published in August 2016, that has demonstrated that monitoring and management of medicine's safety for human use throughout their life cycle have been significantly strengthened with the introduction of new pharmacovigilance processes after the new legislation which came into effect in July 2012.

Then the work focuses on the Risk Management Plan (RMP), a document specifically on the safety profile of a medicinal product whose main purpose is to identify the risk minimization measures, necessary to manage both the identified and potential risks in pre- and post-authorization as well as detailing binding commitments on how they will be monitored for safety and actions to be taken to provide evidence where it is lacking.

Finally the RMP of Vardenafil has been filled and assessed in order to test the utility of this tool for the pharmacovigilance.

Keywords: Risk Management Cycle, PRAC, Risk Management Plan, Generic Medicinals.

The issue of literature duplicates from RNF

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ABSTRACT

Background: As expected from GVP 6, Pharmaceutical Companies are required to monitor the scientific literature systematically in order to identify new drug safety signals. They must identify and register individual case safety reports (ICSRs) from spontaneous reports or post-authorization non-interventional studies. If more medicines are mentioned in the publication, only those that are identified by the author of the publication and who have at least a possible causal relationship with the suspect adverse reaction should be taken into account. Pharmaceutical companies must monitor all active substances for which they hold a marketing authorization in the EU market. The articles must not be considered for the creation of an ICSR if the suspect drug is not a medicinal product of their membership. In the absence of a specified product, Companies must realize ICSR considering active substances of their relevance.

Objective: All Marketing Authorization Holders are required to enter all reports of suspect adverse reactions related to Italian cases published in the literature and not covered by the monitoring service of literature by the EMA provided for by Article 27 of Regulation (EC) No. 726/2004 in the National Pharmacovigilance network. Since December 2015, all cases made are visible for all. Therefore, the problem of identifying duplicates occurred, for service companies as ASGENIA because the interpretation that is often given to a scientific article appears to be different between the various owners to the Marketing Authorization Holders. In recent months, my daily task has been to perform search of literature duplicates in order to identify critical points of this job and resolve them.

Results: Every day in ASGENIA we made research of duplicate for individual Pharmaceutical Companies on the database "Safety drugs". The purpose is to identify the literature cases, which have been already processed and then transmitted to Pharmaceutical Companies. First of all, the references of the source numbers are compared to assess possible duplicates of each other and then on each card a double investigation in the database is made. The first for title of the scientific article and the second for first author, in order to avoid errors due to incorrect transcription of references. Possible duplicates are analyzed one by one, considering the equality of references, patient data, drug and adverse reactions.

Conclusions: It is sometimes complicated for companies as ASGENIA do research of duplicates. In fact cards duplicate between them have often adverse reactions encoded differently or drugs that are sometimes considered suspect and other concomitant. Therefore, the search may not be easy, which is why it always requires a comparison between two operators. In order to avoid many duplicates, Pharmaceutical Companies should not re-enter the same cases made from other companies in the network, but AIFA imposes this system. If Pharmaceuticals Companies take a literature case from the Pharmacovigilance network and process it, what is the meaning of reinsert later the same case, in their own name in RNF?

KEYWORDS: Literature duplicates, Pharmacovigilance network, Scientific literature.

Preventability of gliclazide-induced serious hypoglycaemia: a retrospective study based on real safety data from Italy

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ABSTRACT

Background: Hypoglycaemia is the most common side effect related to antidiabetic therapy; responsible of serious negative clinical outcomes, both in the short term and in the long term. In addition to the clinicians' concerns, the social and economic impacts of serious hypoglycaemias are considerable too.

Objective: To assess the preventability of gliclazide-induced serious hypoglycaemia based on real world safety data from Italy, byP-method, an innovative preventability assessment method, introduced by WHO and aiming to the identification of risk factors that increase the likelihood of ADRs.

Results: Sixty-nine ICSRs were considered: 4 life-threatening cases (5.8%); 45 cases (65.2%) with outcome of hospitalisation; 20 cases (29.0%), reported as medically relevant. The patient age average was 81 years; the concomitant drugs average, excluding gliclazide, was >4 for patient. Fifty ICSRs were evaluated as preventable (72.5%), 13 ICSRs as non-preventable (18.8%), 6 cases (8.7%) as non-assessable. The preventable hypoglycaemias were mainly related to employment of contraindicated drugs, incorrect dosages or an inappropriate choice of antidiabetic in view of the patient's clinical conditions or patients non-compliance.

Conclusions: A significant rate of serious hypoglycaemias are preventable and are often related to inappropriate prescription or non-compliance to the treatment by the patient. A thoroughly and continuous medication review, combined with an adequate patient education can significantly improve both patient and HCP awareness. The benefits would be either clinical, social and economic, considering the relative rates of hospitalisation and the related costs.

KEYWORDS: Hypoglycaemia, Gliclazide, Preventability, P-method.

Handling of a Pharmacovigilance CAPA Plan: a challenge to improve the company awareness

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ABSTRACT

Background: The scope of drug safety surveillance is expansive and is becoming increasingly complex because the safety of a medicine is related not only to its pharmacological properties but also to how it is used in actual practice and to the integrity of the product's quality throughout the supply chain. An instrument to assess the compliance to the Pharmacovigilance requirements by the pharmaceutical industries are the inspections conducted by the competent authorities.

Objective: This paper provides an overview of the findings of a MHRA (UK Regulatory Authority) Pharmacovigilance inspection occurred in June 2016 to a multinational company with headquarter in Italy and the corrective/preventative actions that were put in place in order to solve the findings.

Results: We describe the concerned area of the deficiency and actions proposed. The main topics covered by the inspection findings were the quality pharmacovigilance system and the maintenance of its performance, the collection and collation of ADRs, the staff training and the engagement of the upper management.

Conclusions: Inspections are a chance for the company to demonstrate regulatory compliance and an opportunity to improve its pharmacovigilance system, because we have to remember that the goals of the company and inspectors are the same: to protect public health.

Keywords: Quality system, GVP, Pharmacovigilance inspection, CAPA plan, Finding.

Campania Preventability Assessment Committee: a focus on the preventability of non-steroidal anti-inflammatory drugs' adverse drug reactions

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ABSTRACT

Objective: This study aims to investigate preventability criteria of adverse drug reactions (ADRs) involving non-steroidal anti-inflammatory drugs (NSAIDs) by analysing individual case safety reports (ICSRs) sent through Campania region spontaneous reporting system from July 2012 to October 2016.

Methods: For all the ICSRs that reported NSAIDs as suspected drug, a trained multidisciplinary team of Campania Pharmacovigilance Regional Centre composed of pharmacists and clinical pharmacologists with pluriennial experience in Pharmacovigilance assessed preventability by using the P-method.

Results: Overall 19,039 ICSRs were sent to Campania Pharmacovigilance Regional Centre, of which 550 reported NSAIDs as suspected drug. In total, 94 cases (17.1%) out of 550 ICSRs were preventable. In the 94 preventable cases, 201 critical criteria were detected of which 182/201 (90.5%) related to healthcare professionals' practices, 0/201 (0.0%) to drug quality, and 19/201 (9.5%) to patient behaviour. The most detected critical criteria were the necessary medication not given (52/182; 28.6%), labelled drug-drug interaction (36/182; 19.7%), incorrect drug administration duration (31/182; 16.9%), wrong indication (26/182; 14.2%), therapeutic duplication (18/182; 10.0%), and documented hypersensitivity to administered drug or drug class (10/182; 5.6%). In seventeen (18.1%) preventable cases, there were 19 critical criteria involving non-compliance (15/19 critical criteria; 78.9%) and self-medication with the non-over-the-counter drugs (4/19 critical criteria; 21.1%). In all, 17 out 94 (18.1%) preventable cases involved over-the-counter drugs.

Conclusion: A call for action for Campania Pharmacovigilance Regional Centre is necessary in order to promote initiatives to increase the awareness of healthcare professionals and citizens on the risk associated with inappropriate use of NSAIDs.

Keywords: Adverse events, Preventability NSAIDs, Spontaneous reporting system, Campania region.

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HPV vaccine: nine years of monitoring on the Italian National Pharmacovigilance Network

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ABSTRACT

The Human Papillomavirus (HPV), often asymptomatic, is a virus that can lead to a wide spectrum of lesions. Some types of HPV can cause cervical cancer in women and the WHO declared this virus necessary cause for the development of the disease.

Three vaccines are available: Cervarix®, Gardasil and Gardasil-9 (respectly bivalent, tetravalent and ninthvalent) and they work by preventing infections caused by the most common types of HPV. On 2007/2008, Italy launched a free and active vaccination campaign aimed at girls aged 11-12 and some regions have included girls whit other age (under 25). Vaccination in young males (11-12) and in patient HIV-positive has been recently approved in some regions. This is part of the new Italian Vaccination Plane 2017/2019.

We analyzed AE report from the Italian Network of Pharmacovigilance (RNF), about years 2008-2016 (with a focus on 2016), extrapolating both serious and not serious ADRs regarding Cervarix®, for which GSK is the holder of marketing authorization. The purpose of this experimental project is to characterize these reports focusing on several aspects. Finally, we matched the analysis results with the safety information reported in SPC (Summary of Product Characteristics).

Keywords: Human Papillomavirus (HPV), Italian network of pharmacovigilance (RNF), Cervical cancer, Vaccination campaign, Safety.

Clozapine in patients with Alzheimer's disease: monitoring of prescriptions in ATS Città Metropolitana of Milan in 2015

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ABSTRACT

Background: Clozapine is an antipsychotic drug belonging to the class of second-generation antipsychotics. The indications approved and included in the Technical Specifications of medicines based on clozapine are schizophrenia and psychosis in Parkinson's disease. Therefore, the use of this drug in patients with dementia is an off-label use. For this reason the prescription must be made through authorized specialist centers identified by the regions, and the reimbursement procedure, by the NHS, in direct distribution system.

Objective: To verify the presence of NHS prescriptions for drugs based on clozapine in patients taking drugs for Alzheimer's disease (AIFA Note n. 85), in absence of other diseases that justify the prescription of drug with NHS prescription, in order to evaluate the appropriate prescribing.

Results: From the monitoring of prescriptions of clozapine and drugs in AIFA Note n. 85, in 2015, 46 patients have prescriptions for both these medications. 54.3% of these patients have exemption for Parkinson's Disease or Psychosis, 23.9% is in possession of Block Disability (IC14 and IC13) or Chronic Disease (E30). For all these patients the prescription of clozapine can be considered appropriated, despite the simultaneous presence of Alzheimer's disease. Instead, for 21.7% of subjects the NHS prescriptions of clozapine and drugs in AIFA Note n. 85 could be considered improper.

Conclusions: Despite AIFA Communications during the past 10 years, regarding the use of clozapine in patients with Alzheimer's disease, have reiterated the need for active surveillance, resulting in disbursement of antipsychotics in direct distribution regime, in our reality there are some cases of probable improper prescribing. In this context, it emerges the crucial role of territorial pharmaceutical service in monitoring the appropriate prescribing.

Keywords: Clozapine, Alzheimer Disease, Appropriate prescribing.

Quality Assurance in Pharmacovigilance: a Company Audit experience

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ABSTRACT

This article is about Quality system and Quality Assurance in the Pharmacovigilance area, concepts introduced with the publication of Directive 2010/84/EU and Regulation 520/2012. Moreover, Pharmacovigilance Quality System is closely linked to Good Pharmacovigilance Practice. GVP module IV provides guidance on planning and conducting the legally required audits.

The aim of this project is to describe an audit preparation and management, concentrating on the experience of Janssen Pharmacovigilance Audit.

I have consulted Janssen Cilag Work Instruction and Standard Operation Procedures relevant to the subject and Good Vigilance Practices module IV. Then, I focalized the attention on LOC audit of Janssen-Cilag: Country office Audit Overview, Pre-Audit Request for Information (RFI), data from Janssen's SharePoint and audit final report. I elaborate data from SharePoint to make it easily understandable.

A routine Local Operating Company (LOC) audit of Janssen-Cilag Italy was performed by the Headquarters' department Bioresearch Quality Compliance (BRQC). Starting from Audit scopes, we present some items discussed with the Pharmacovigilance Manager of the LOC. The main purpose was to assess compliance with regulatory requirements, contractual agreements, and company policies and procedures. For that purpose, auditors have requested to review documentation, to demonstrate systems in place and to go to the LOC office facilities. Audit final report cannot be shown due to data confidentiality, so the paper concentrates on preparation of audit and on the way the results have been presented and argued by auditors and auditee.

The attention focuses on Pharmacovigilance Agreement, Global Medical Safety case receipt and submission of expedited adverse events report to the Local Competent Authority. Compliance data and findings are discussed.

Audit is a relevant activity to check quality in pharmacovigilance, concept that has to be intrinsic in Pharmacovigilance System. In fact, Pharmacovigilance operations results are measured by Quality Assurance to indicate the way for a continuous improvement.

Keywords: Pharmacovigilance system, Quality system, Audit, Checklist.

Study of the Adverse Reactions of Biological Drugs used to treat Inflammatory bowel disease (IBD)

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ABSTRACT

Background: The intrinsic variability of molecules and the complexity of biological drug production techniques make it even more difficult to predict any adverse reactions that may occur during both clinical trials and clinical practice. Although it is true that a biological drug represents the turning point in the treatment of many pathologies for which traditional drugs have proved insufficient or sometimes ineffective (such as in many immune diseases, including IBD inflammatory bowel diseases such as Crohn's Disease and Ulcerative Colitis), it is equally true that its management is considerably more complex than purely chemical-physical, pharmacological and regulatory, as far as safety surveillance is concerned. Although clinical trials have shown a good safety profile of biological drugs, there are no reliable data on the safety profile of long-term. Late toxicities are not reported and are often underestimated.

Objective: The objective of the study conducted personally is to analyze the data collected on the treatments carried out and monitored from June 2014 to December 2016 and to evaluate the incidence of ADRs in patients with gastroenterological diseases treated with specific drugs such as Infliximab, Adalimumab, Golimumab, Vedolizumab and Remsima®.

Results: For the 82 patients enrolled in this study, recruited in the Gastroenterology Unit of Mater Domini University Hospital of Catanzaro, Annunziata Hospital of Cosenza and the San Giovanni di Dio Hospital of Crotona, 88 therapeutic cycles of biological drugs were administered. In particular, 61 therapeutic cycles of infliximab, with 36 adverse events (59%); 19 therapeutic cycles of adalimumab, with 9 adverse events (47%); 5 treatment cycles of golimumab, with 3 adverse events (60%), one therapeutic cycle vedolizumab with one adverse event (100%) 2 therapeutic cycles of Remsima®, with one adverse event (50%). Following administration of 88 treatments, there were only 2 serious ADRs. According with literature data, infliximab is associated to more side effect than adalimumab. Among the most common adverse reactions reported were, in order of incidence: headache and weakness (16%), fatigue (14%), joint pain (10%), rash and allergic reaction (6%), psoriasis, pruritus, hyperhidrosis, urticaria, dizziness, drowsiness, flushing, back pain, leg heaviness, aching ends, suffocation (4%). These results coincide with what has been reported in the literature.

Conclusions: In conclusion, from the analysis of data it is noted that after the administration of 88 treatments only in 8 cases the therapy was suspended due to the occurrence of ADRs (9%, in most cases the suspension of medication or switching to other therapeutic line was due to the ineffectiveness of the biological drug and the side effects of the drugs were well tolerated) and there were only 2 serious ADRs. Therefore, this study also shows that biological drugs are relatively safe while the problem of underreporting remains.

Keywords: Biological therapies, TNF- α antagonist, IBD, Adverse drug reaction, Pharmacovigilance.

Regional Monitoring Registries for evaluation of Adverse Drug Reactions

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ABSTRACT

Background: The Italian monitoring registries represent advanced tools to control the appropriateness of prescriptions and use, the safety profile, and the effectiveness of certain drugs. However, at regional level it is not possible to analyze these data even though they should be available to evaluate appropriateness and monitor expenditure. Thus, in this context, Veneto has activated its own registries: a monitoring registry of biological drugs and a database, called NAVIGATORE, for the new direct-acting antivirals (DAAs), for the treatment of hepatitis C.

Objective: Evaluating the Adverse Drug Reactions (ADRs) found in registries, and recording them into the National Pharmacovigilance Network (NPN) it was possible to understand registries situation. Once identified the reports type, an analysis was carried out through VigSegn with the purpose of integrating the missing ones as new information in the NPN.

Results: This project enables to detect 14 ADRs in biological registry, and put 6 of them in the NPN; finding 137 reports in NAVIGATORE database, and record 132 of them in the NPN.

Conclusion: Although in a different manner, both regional registries can be considered as a valid regulatory instrument that could contribute to assess safety and benefit/risk profile of drugs. From an evolutionary perspective, a considerable effort would be integrate regional registries with a section that allows to automatically transfer ADRs to the NPN, in order to preserve precious information.

Keywords: Regional monitoring registries, Adverse Drug Reaction, AIFA registries, VigSegn.

Signal management in pharmacovigilance. An example of signal detection methodology

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ABSTRACT

Objective: The aim of this project was to illustrate the process of evaluation and analysis of potential safety signal arising from reports of adverse events retrieved from any source and stored in the Pharmacovigilance Database. The evaluation of safety signals is part of routine pharmacovigilance and it is essential to ensure that Regulatory Authorities have the most up to date information on a medicine benefits and risks.

Methods: A qualitative method has been applied to perform the signal detection. The periodic review and analysis of signals was performed using line listings and frequency tables generated from the Pharmacovigilance Database and the sales data provided by the client covering the period under analysis. Any detected signal was assessed for its impact on the risk benefit balance of the product and population safety. An immediate re analysis and actions were performed if its impact was judged as significant.

Results: A total number of 197 adverse events (AEs) related to the active ingredient adrenalin and a total number of 48 AEs related to active ingredient noradrenalin were recorded in the Pharmacovigilance Database covering the analysed period. The most represented and recurrent AE collected for both active ingredients was "Stress cardiomyopathy", included in the System Organ Class (SOC) of "Cardiac disorders". This serious AE was assessed as unlisted according to the current version of Client SmPC. In 2014 and in the first semester of 2016 were collected 5 ICSRs containing the event "Stress cardiomyopathy" and associated to adrenalin, while in 2015 only 3 ICSRs were recorded in the Pharmacovigilance Database. The same adverse event associated to noradrenalin was retrieved only in 2015 and the ICSRs collected were two. Another serious and unlisted adverse event was revealed by the scientific literature search. The AE experienced by patients (22 ICSRs) following adrenalin administration was "Extraocular muscle paresis", included in the SOC of "Eye disorders". Taking into account AEs collected and sales data in the considered period, there was no evidence of a frequency increase of AEs assessed as listed according to the Client SmPC for both the active ingredients.

Conclusion: No new risk or risk that can change risk benefit balance of the considered medicinal products have been detected. The new unlisted AEs will be kept under continuous monitoring.

Keywords: Signal detection, Adrenalin, Noradrenalin, Stress cardiomyopathy, Extraocular muscle paresis.

Pharmacovigilance in oncology: evaluation of chemotherapy-induced adverse drug reactions

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ABSTRACT

Background: Chemotherapeutics drugs are extremely beneficial for cancer treatment but they cause a multiplicity of ADRs. The under-reporting is relevant problem in oncology where the toxicity of these drugs is often considered “normal” or “inevitable”. The occurrence of “non-serious ADRs” are seldom critically evaluated but they have a negative impact on patients’ quality of life.

Aim: to conduct a qualitative and quantitative analysis of oncologic ADRs and enhance the culture of pharmacovigilance between the oncologists.

Methods: We analysing medical record of oncologic patients and ADRs were codified using MedDRA dictionary and reported in the Pharmacovigilance National Network. The severity assessment was made according to the WHO Critical Term List. The ADRs notoriety was provided in the Summary of Product Characteristics and for unknown ADRs was conduct a literature research. A specific report was prepared and made available for the physician. The causality assessment was established using Naranjo Algorithm.

Results: We analysed 72 ADRs reports coming from 54 patients of which the 37 female and 17 male. ADRs mostly occurred in the age group of 61-80. The 95.8% of ADRs were caused by chemotherapy drugs and 1.4% was caused by chemotherapy complementary therapy. The 72% of ADRs were considered serious and the 28% were non-serious. Female developed the 50% of serious ADRs and 19% of non-serious ones compared to the male. The outcome was full resolution for the 56.94% of patients, improvement for 34.72%, adverse reaction unchanged or worsened for 6.94%, outcome not yet available for 1.39% of patients. The 97.22% of ADRs were known, while only 2.78% were unknown. Gastrointestinal disorders and Skin and subcutaneous tissue disorders (16.13%) were the SOC most involved. Causality assessment revealed that the 98% of the adverse reactions were possible and only 2% probable. The most common ADRs were alopecia (24.62%), erythema (5.03%), asthenia (4.52%), paresthesia (4.02%), nausea (3.52%), itch (3.02%) caused principally by paclitaxel, oxaliplatin, carboplatin, doxorubicin, and cyclophosphamide.

Conclusion: This work demonstrates that the presence of trained personnel can contribute to sensitize the culture of pharmacovigilance between oncologists, determining a significant increase of number and quality of chemotherapy-induced ADRs. Data produced can help in generating both of signals of rare and unsuspected adverse effects (providing additional information about risk/benefit profile of a drug), and in the reporting of events that, although not severe, however, may affect the already fragile patient’s quality of life.

KEYWORDS: Oncology, Pharmacovigilance, Chemotherapy, Under-reporting, Adverse drug reactions.

Overview on safety reporting for a Non-Interventional Post Authorization Safety Study conducted in Italy

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ABSTRACT

Introduction: the pharmacovigilance system, both in Italy and Europe, has undergone profound changes. Basically, the changes tend to increase the efficiency, speed and transparency of pharmacovigilance activities.

New regulations require improved safety reporting in post-marketing studies including Non-Interventional Post Authorization Safety Studies (NI-PASS) that are designed to ensure that medicinal products are monitored for long-term safety in more extensive patient populations.

Methods: pharmacovigilance data received from Non-Interventional Post Authorization Safety Study, must be managed through well-defined Individual Case Safety Reports (ICSRs) process.

Sanofi established a Pharmacovigilance organization working in accordance with various Standard Operating Procedures (SOPs) and international/local legislation requirements in order to ensure safety surveillance for patient and subject's protection.

Results: the investigators collect data on treatments received by patients and their health status in routine clinical practice reflecting the real-life utility of drugs, he is responsible to reports two types of safety reports, those originating from unsolicited and solicited sources.

Therefore, the fact to have a double reporting (via solicited and unsolicited) and multiple actors involved in the process of reporting do not exclude to face off discrepancies in Adverse Drug Reaction (ADR) reporting.

Discussion: The sponsor procedures aim to reinforce the system of pharmacovigilance, to implement several strategies to increase the quality of ADR reporting and to avoid possible discrepancies.

Keywords: Non-Interventional Post authorization Safety Study, Adverse Drug Reaction, Rete Nazionale di Farmacovigilanza, Individual Case Safety Report.