Riassunti delle relazioni finali dei progetti di ricerca svolti dagli studenti nell'ambito del tirocinio formativo del master per l'anno accademico 2018-2019

Characteristics of drug allergy and anaphylaxis recorded in several Italian Emergency Departments during 2012-2019

Paola Andreetta, Silvia Pagani, Mauro Venegoni, Giuseppe Danilo Vighi

Training held at
Internal Medicine Department, ASST Vimercate, Vimercate, Italy

ABSTRACT

Background: Drug Allergy is a kind of adverse drug reaction that result from a specific immune-mediated response to a medicine. Mereafaps is a pharmacovigilance study collecting data on the ADRs from one hundred Emergency Departments of Italy since 2006. To identify the number of allergic drug reactions and the cases of anaphylaxis in the Mereafaps database from 2012 to 2019 to determine the characteristics and clinical features.

Methods: A retrospective observational study has been conducted, reviewing all allergic ADRs admitted in Mereafaps database between January 1st, 2012 and November 1st, 2019. ADRs have been identified by the appropriate med-DRA code, to find drug allergy and anaphylaxis cases. Demographic data, the kind of reaction, the seriousness and the use of adrenaline in anaphylactic events during the period under review have been evaluated.

Anaphylactic events have been analysed separated from the other allergic ADRs.

Results: During the interval 2012-2019, 13,532 cases of allergic drug events and 548 of anaphylaxis have been collected. Women are more than males (respectively 59.5% and 52.6% of anaphylaxis and of allergic ADRs). The mean age is 45.9 years old for allergic events and 55.7 for anaphylaxis. 60% of anaphylaxis cases is associated with antinfectives, 14.4% with anti-inflammatories, 7.7% with contrast media, 5.3% with analgesics, and 3.8% with antineoplastic drugs. There are three fatal cases, two women of 85 and 90 years old respectively, and a 42- years-old man, all with anaphylactic shock with anti-infectives (levofloxacin, ceftriaxone and amoxicillin clavulanate). Most cases of anaphylaxis have been treated with steroids and antihistamines, 322 patients (59%) have been treated with adrenaline too. The percentage of the treated with adrenaline varied in the years, without a clear trend.

Comparing the cohort of allergies and of anaphylaxis we can observe some difference in the substances more frequently involved: in the anaphylaxis the more reported is amoxicillin with clavulanic acid, followed by ceftriaxone, amoxicillin, diclofenac and ketoprofen, whereas in the allergies amoxicillin (with or without clavulanic acid) is followed by ketoprofen, ibuprofen and paracetamol.

Conclusion: The Emergency Departments are a good point of observation for allergic drug events; antibiotics are by far the most reported substances, followed by anti-inflammatory drugs. Most of the anaphylactic cases were treated with adrenaline, in addition to steroids and antihistamines, but there is still an underuse of it.

Keywords: Adverse Drug Reactions (ADRs), Anaphylaxis, Allergy, Adrenalin.

Challenging the future in Pharmacovigilance: where we are and where we are going

Lucia Broggi, Valentina Calderazzo

Training held at
Boehringer Ingelheim, Via Giovanni Lorenzini 8, Milan, Italy

ABSTRACT

Background: The common goal among the pharmaceutical company, healthcare professionals and regulatory agencies is patient's and public health. In line with the objectives and definition of pharmacovigilance (PV) outlined by the WHO, how can PV department of Marketing Authorization Holder (MAH) contribute to achieve this common goal? Significant transformations happened over the last years regarding the role of PV departments in pharmaceutical company. The PV paradigm is changing and evolving very fast, keeping up with all the new developments in artificial intelligence, the analysis of real-world data to obtain real world evidence, and the multiple, really diverse sources of safety information that are available today. This had an important impact on both Adverse Event management, on type of activities and how to interact with the PV stakeholder.

Aim: The objective was to evaluate the potential correlation between training and PV awareness activities and the trend of domestic reports in years impacted by major changes. What could be the challenges and opportunities in this context for pharmacovigilance function in a pharmaceutical company?

Methods: Training and PV awareness activities intended to raise awareness on pharmacovigilance topics carried out in Boehringer Ingelheim Italia SpA (BI) were mapped from 1 January 2017 to 31 December 2019. An analysis considering also stakeholder involved has been performed. In particular, we analysed the PV-awareness activities, which aimed to strengthen the knowledge of pharmacovigilance requirements, both inside and outside the company. The involved functions have been divided in function with potential PV impact without direct contact with HCP (Health Care Professional) and function on the field with direct contact with the HCP. In order to perform an assessment of the effectiveness of PV awareness activities, these have been related with the trend of domestic reports received during the period considered.

Results and Conclusions: This analysis highlighted that the number and the type of activities are changing. In 2017, most of the activities were related to face-to-face training, whereas in 2018 all basic training has been switched to digital learning, while courses for specific functions or activities have been maintained and an initial increase of PV awareness activities is visible. In 2019, the PV-awareness activities have been significantly increased.

The enhancement in awareness activities resulted in a significant increase in domestic reports starting from the first quarter of 2018 and it ensured that the trend has been maintained. Therefore, our analysis highlights the need to reinforce awareness with targeted activities to improve the reporting of AEs and in general to obtain a better consciousness about PV.

Keywords: Patient safety, PV-awareness activities, Social media, Training.

Pharmacological analysis of interactions between antiretroviral therapies and dietary supplements

Isabella Bronzino, Dario Cattaneo[1,3], Cristina Gervasoni[2,3], Sonia Radice[1]

Training held at:
[1] Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy
[2] III Infectious Disease Unit, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy
[3] Gestione Ambulatoriale Politerapie (GAP) Outpatient Clinic, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy

ABSTRACT
Introduction: As the life expectancy of HIV positive patients increases, so does the desire to improve their quality and physical and mental well-being. In pursuit of these goals, HIV-positive patients, such as HIV-negative patients, increasingly use unconventional approaches that are generically referred to as CAM (complementary and alternative medicine).
Aim: The aim was to assess how CAM could affect the plasma concentration of antiretroviral drugs in HIV positive patients, leading to the failure of antiretroviral therapy.
Methods: The study was conducted at the GAP (*Gestione Ambulatoriale Politerapie*) of ASST Fatebenefratelli-Sacco belonging to the Department of Infectious Diseases, using an internal database to identify patients who were taking concomitant CAM treatment and showed detectable viral load. The mechanism of identified DDI has also been studied.
Results: An increase in viral load was found in the three patients surveyed, i.e. a failure of the TARV to which they are subjected. Through a pharmacokinetic analysis-it was possible to evaluate that this problem was due to the interaction between food supplements and antiretroviral therapy. In the three patients the viral load of HIV, evaluated a few weeks after the suspension of these products, was undetectable.
Conclusions: This evidence shows that dietary supplements should be used with caution in patients with HIV infection treated with lipophilic antiretroviral drugs because of the risk of virological failure. In this view, it is necessary that all professionals involved in the management of HIV-infected patients should carry out a careful evaluation of all therapies, both conventional and non-conventional, in order to prevent unexpected failures of antiretroviral therapy from appearing.

Keywords: Antiretroviral drugs failure, DDI, Alternative Medicine, CAM.

Statin prescription in the Puglia Region: attempts to contain costs and interventions to promote appropriateness

Mariangela Calcagno, Sharon Natasha Cox, Maria Cristina Carbonara, Paolo Stella

Training held at
Apulian Regional Health Department, Bari 70126, Italy

ABSTRACT

Background: The Apulian Regional Council with Order n. 2034 of 13.12.2016, published on BURP n.5, supplement of 12.01.2017, has disposed a series of initiatives aimed at bringing the regional prescriptive trend back to the national average. The aim of this measure was to contain the agreed expenditure relating to the category of lipid-lowering agents, in fact, in the Puglia Region, the expenditure relating to these drugs is 80% higher than the national average, according to the Italian National Reports of medication use (OSMED, 2018)1. Provision 2034/2016 was implemented for the prescription monitoring of high cost lipid-lowering drugs and consequently lower the regional pharmaceutical expenditure. During 2018, the active ingredient ezetimibe in preconstituted association with simvastatin, and the active substances rosuvastatin and ezetimibe, in monotherapy, were included in the AIFA transparency lists, with consequent change in the scenario of costs related to statin-based drugs. Ezetimibe in monotherapy or in association with statins are currently the most expensive therapeutic choices with the highest incidence on the agreed pharmaceutical expenditure therefore it is necessary to monitor these prescriptions.

Aim: In this study, our main aim was to evaluate lipid lowering drug prescription trend in the Puglia Region from 2017 to 2019; at first, we evaluated the drugs sales in a pharmacy in Palagiano, a little town in the province of Taranto. Then we moved on to the evaluation of statin prescription in the Puglia Region and verified whether the pharmaceutical expenditure for these medicines reached the national average, also considering their inclusion in the AIFA transparency lists. Another aim was to evaluate if there was a difference in adverse drug reactions between NO co-payment and co-payment drugs.

Results: The total per capita co-payment expenditure in Puglia Region is more than two times higher than the national average. Atorvastatin, simvastatin and rosuvastatin were the most prescribed in the year 2019, respectively 56%, 19% and 16%. Atorvastatin and rosuvastatin have the highest potency and their prescriptions were more than two times greater compared to lower-potency statins (fluvastatin, lovastatin, pravastatin and simvastatin) (72% Vs 28%). The prescribing activity is greater for co-payment products (61.55%) compared to NO co-payment ones (38.45%) Furthermore, when we focused our attention on the cost of lipid-lowering drugs (including ezetimibe in monotherapy and associated with simvastatin), we find that 74.60% of the prescriptions concern low-cost products, while 24.40% relate to high cost drugs. The per capita expenditure relating to low-cost products is 7.4 euros, a value that is higher compared to both the OSMED average (6.1 euros) and our regional target (6.4 euros). This does not occur for high-cost products, where the per capita expenditure is lower than the OSMED average (3.8 Vs 5.3 euros) and its value equals our regional target. The prescribing activity is greater for co-payment products compared to NO co-payment ones (61.55% Vs 38.45%), but we found that the latter give less ADRs than co-payment drugs.

Conclusions: Our study demonstrates that, in the face of greater prescribing activity relating to co-payment drugs, the latter do not give the guarantee of minor ADR, highlighting the need for more information of physicians on the risks connected to inappropriate prescription of lipid-lowering drugs and on their burden on the regional expenditure, given the large population of patients treated with these drugs in the Puglia region.

Keywords: Lipid-Lowering Drugs, Co-Payment, Adverse Drug Reaction (ADR).

Medical device post-market vigilance and surveillance in the light of the new EU regulation: the impact of the new requirements on a medical device distributor

Alice Cecchinato, Chiara Pozzato[1], Sebastian Neuss[2], Fulvia Feltrin[1]

Training held at
[1] PharmaLex Italy - Milan (Mi), Italy in partnership with
[2] YES Medical Device Services GmbH, a PharmaLex company, Germany

ABSTRACT
Background: With the entry into force of the new EU Regulation, the MDR 2017/745, which shall be applied from 26th May 2020, stakeholders dealing with medical devices shall be compliant with the new requirements introduced.
Aim: The scope is to analyse the main changes in comparison to the previous legislation and the practical effect they will have on the system, especially from a post-market vigilance and surveillance perspective. The starting point is a client's request: which is the impact of the new Regulation on a medical device distributor and how to organize the vigilance and surveillance system in the light of the new requirements? This work allowed us to reflect on how to embrace practically the changes introduced by the new Regulation, proposing a generic approach intended to implement the current system with the new requirements.
Methods: For the scope of our work, we considered all the sources available to define the previous medical devices legal framework and to draw the new legal setting, such as the national and European legislation, EMA and the Italian Ministry of Health official statements. Using the plan-do-check-act approach, we described a scheme of activities the distributor shall perform, differentiating two scenarios: a pure distributor and a distributor who assumes the manufacturer's obligations, in accordance to article 14 and 16 of the new Regulation.
Conclusion: The new requirements introduced by the MDR 2017/745 have increased the workload requested to stakeholders involved in the medical devices. It appears evident that the major impact of the Regulation is on the manufacturer: the number of tasks requested is more significant and strictly regulated than before. Also, on the figure of a pure distributor the number of tasks requested are higher but, in somehow, it could be argued that most of the activities described in article 14 of the Regulation are activities that a well-functioning distributor (with a good quality system in place) would have carried out regardless of the new legal requirements. However, in response to the increased workload, it is expected also an increase in the safety and transparency around medical devices, but only future analysis will confirm that.

Keywords: Regulation (EU) 2017/745, MDR 2017/745, Medical devices, Post-market vigilance and surveillance, Distributor.

Regulatory Authority inspections in Pharmacovigilance: European and American Authorities comparison and similitudes

Giuseppina C. D'Amico, Francesco Belli, Laura P. Boga

Training held at
Headquarters of Dompé farmaceutici S.p.A. Milan, Italy

ABSTRACT

Background: Safety of drugs is of utmost importance to patients and healthcare professionals. The pharmaceutical industries have an ethical and legal responsibility to ensure that the products they market do not harm the patients they are intended for and that the Benefit/Risk profile is maintained positive. The repercussions of a drug found to have a negative safety profile are enormous for patients, healthcare professionals and the industries. Regulatory bodies that approve marketing authorisations have a responsibility to protect public health through the continuous monitoring of drug safety; Marketing Authorization Holders (MAH) collect, collate, process and analyse adverse drug reactions to maintain a continuous overview of the safety profile of their medicines and highlight potential risks. There are specific rules in place in all countries, with defined role and responsibilities for regulatory authorities and MAHs. In line with regulatory requirements, Regulatory Authorities conduct pharmacovigilance inspection in order to assess the compliance to law requirements and pharmacovigilance obligations of the MAHs or any organization providing pharmacovigilance services to MAHs. Main objective of the regulatory inspections is to determine that the MAH has personnel, system and facilities in place to meet their pharmacovigilance obligations and to identify, record and address non-compliance which may pose a risk to public health. Inspection results may be used as a basis for enforcement action, where considered necessary. Inspections are conducted according to specific guidelines and rules, respectively in force in the EU and in the American territory, and the MAH shall be fully aware of the regulations before hosting an inspection. Regulatory requirements shall be duly reflected in company procedures and there must be evidence that pharmacovigilance processes are performed in compliance with regulations and company procedures.

Aim: To analyse the different types of inspections (both EMA and FDA inspections) that can involve the pharmacovigilance department, rather performed by the European or the American inspectorate.

Methods: To gain knowledge of the inspection process and to get the inspected team familiar with the same, specific trainings and mock interviews are generally performed with concerned company personnel who most probably will participate to the inspection, either in the front or in the backroom, before the inspection. An effective preparation both of the team and the dedicated rooms is essential for the inspection. Before hosting the AIFA inspection, the Good Pharmacovigilance Practices (GVP) and the European legislation in the field of Pharmacovigilance have been carefully reviewed and mock interviews performed by qualified personnel. For the American FDA inspection, the Food and Drug Administration guideline have been reviewed, ad hoc training received, and mock interviews performed.

Results and Conclusion: In conclusion our analysis showed that the approaches in inspections by the two Authorities are mainly different. However, they share some common aspects.

The inspection process itself may vary between the two regulatory bodies, based on the inspector habit, background and rules, although the general aim is the same: to verify MAH compliance and to protect public health.

Keywords: Drug Safety, Pharmacovigilance inspection, EMA, FDA, Comparison and Similitudes.

Monitoring of adverse reactions following the use of food supplements

Ascanio De Blasiis, Gian Nicola Castiglione

Training held at
Chiesi farmaceutici S.p.a., Italy

ABSTRACT

Background: Food supplements are made up of nutrients and substances with a nutritional and physiological effect and they are formulated to obtain a precise effect on the human organism through the integration of the diet. The use of these products is continuously increasing thanks to their efficacy in the treatment of both small and chronic and / or degenerative pathologies that are difficult to solve with real medicines. Although legally considered to be food products, market experience has shown the ability of food supplements to trigger adverse reactions exactly like medicines.

Aim: The aim of this work is to propose a surveillance system for food supplements that allows managing and characterizing the adverse reactions related with their use. This system allows the cases related to food supplements, ensuring compliance with the laws in force and provides the tools to create and monitor their safety profile. Through the complete management of cases relating to these products, this system allows to guarantee compliance with the laws in force and provides the tools to create and monitor their safety profile.

Methods: We have generated a flow of information that begins with the detection or reception of data relating to the safety of a food supplement; subsequently, these are prioritized based on their characteristics. This information must be entered into the database and evaluated by a doctor in order to perform an analysis of the events reported. Finally, the documents obtained will be archived to be assessed from a qualitative and quantitative point of view.

Results: We have created and putted in place an entire process that allows to receive, evaluate and communicate all the information and any risks deriving from the food supplements adverse reaction (FSAR) report. Unfortunately, no FSAR has come to our knowledge so far to test this system and apply the proposed methodologies.

Conclusions: Food supplements have a high ability to trigger adverse reactions of various degrees of seriousness, both alone and in association. Given the poor characterization of the most common risks associated with these products and the exponential increase in their sales, we believe it is essential to apply some of the methodologies used in pharmacovigilance to this sector. We firmly believe that the use of this system can determine the greater knowledge from a scientific point of view of these products, increase collaboration with the national and European institutions competent in the sector and maximize the benefits associated with the use of products marketed by the company.

Keywords: Food supplements, Adverse reactions, Vigilance system.

EW pharmacovigilance signal detection requirements: EudraVigilance data analysis system (EVDAS)

Chiara Del Grosso, Maria Mammì

Training held at
Asgenia S.r.l., Italy

ABSTRACT

Background: Marketing authorisation holders (MAHs) should continuously monitor the safety of their medicinal products and inform the authorities of any new information that might have an impact on the marketing authorisation. The identification of new risks or changed risks shall be based on the detection and analysis of signals. The Signal management process is a set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed. Safety signal can be detected from a wide range of sources, such as spontaneous reports, clinical studies and scientific literature. Commission Implementing Regulation (EU) No 520/2012 (article 18) requires EMA, national competent authorities and MAHs to continuously monitor the data available in EudraVigilance. EMA and the European Commission have agreed on transitional arrangements to streamline the monitoring of EudraVigilance (EV) by MAHs. on 2018/Feb/22 a pilot period has been activated, during that MAHs of the active substances included in the List of Active Substances involved in the pilot must monitor them in EV (EVDAS) and inform EMA and national competent authorities of validated signals with their medicines.

Aim: The purpose of this project is to describe how Asgenia Srl manages the signal management process in accordance with the current transitional arrangements, particularly the signal detection process, and to examine the criticalities identified with the use of EVDAS.

Methods Signal detection is performed by EVDAS monitoring, through the extraction of eRMR, the selection of DECs by Disproportionality methods, check of the terms of marketing authorisation, download of line listing and finally the analyse case by case the new identified ICSRs.

Results: Two analysis on two different active substances have been performed, thiocolchicoside and levofloxacin, but no signal has been identified. The most important criticalities observed were how to use the big amount of data found with the use of EVDAS and how to select the DEC to analyse.

Conclusions: EVDAS represents an instrument with great potential, but since it is still a pilot project (extension until the end of 2021), there are still no clear and well-defined guidelines on how to use this tool correctly.

Keywords: Signal Management; Signal Detection; EVDAS; eRMR.

Safety data exchange agreement (SDEA). Analysis of the responsibilities and critical issues related to this agreement

Giulia Donatiello, Maria Mammì

Training held at
Asgenia Srl, Roma

ABSTRACT

Background: A Safety Data Exchange Agreement (SDEA) is a contract drafted between the Marketing Authorisation Holder (MAH) and a third party to which the MAH has shared pharmacovigilance activities. A SDEA shall be developed whenever an action is implemented that may impact on pharmacovigilance system or quality system of the MAH. The process leading to the drafting of the document is described and its main key points are then outlined. The first step is represented by the Due Diligence activity, an evaluation of the Third Party that will conduct to the signing of Main Agreement. Once the tasks of each Party have been established, the SDEA can be drafted. Although many different types of agreements can be signed, some essential information shall necessarily be present.

Aims: The purpose of this project is to prove that a Safety Data Exchange Agreement is a flexible contract which varies according to the needs of each specific case, in order to ensure compliance with regulatory requirements.

Methods: The application of Standard Operating Procedures (SOP) has allowed us to define the responsibilities and duties of each party involved in the management of a SDEA.

Results and discussion: Providing some examples of these contracts some cases are afterwards discussed, highlighting particular aspects every time. During the discussion reference is made to current legislation, mostly to GVPs (Good Pharmacovigilance Practices), and to the roles covered by each Party involved. Eventually, attention is focused on the process of reconciliation of data and on some related problems we have faced. Reconciliation is actually the step which ensures not to lose information and that should be carried out involving multiple figures within the company.

Conclusions: The process leading to the definition of a SDEA requests the collaboration of all the parties involved; legislation provides indications on how to enter into the agreement, but then each case requires different arrangements; the document may vary over time and therefore needs to be regularly followed.

Keywords: Agreement, Safety data, Reconciliation, SDEA, Pharmacovigilance.

Analysis of real-world data on treatments for multiple sclerosis: comparison between first line injectable and oral therapies in patients followed by neurological clinic of the "Azienda Sanitaria Universitaria Giuliano Isontina"

Carlamaria Larosa, Chiara Roni

Training held at
Azienda Sanitaria Universitaria Giuliano Isontina, SC Assistenza Farmaceutica Ospedale Cattinara, Trieste

ABSTRACT

Background In the last 10 years the therapeutic approach to the treatment of relapsing-remitting multiple sclerosis (RRMS) has changed radically and new Disease-Modifying Therapies (DMTs) has been developed rapidly. Above all, several oral treatments have shown benefit and have generated much interest because of the convenience of such administration. However, availability of convenient oral drugs will not necessarily translate into clinical effectiveness and safety, but it is necessary collect more information from real life.

Aim The aim of our study was to compare oral and injectable DMTs indicated for RRMS relatively to frequencies and reasons for treatment interruption or therapy switch, to medication persistence and to adherence to treatment.

Method We conducted a retrospective observational study on adult patients affected by RRMS and treated at Multiple Sclerosis Centre of the Neurological Clinic Department in Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI). Patients included in the study were divided into two groups based on the prescribed drug therapy: (1) injectable group, all new patients receiving a first prescription for injectable DMTs in first line therapy during the period from 01/01/2010 to 31/12/2014; (2) oral group, all new patients receiving a first prescription for oral DMTs in first line therapy during the period from 01/01/2015 to 31/12/2019. People enrolled in the study were identified using Business Objects Web Intelligence, a health administrative database. We assessed reasons for any switch or suspension of therapy by analysing medical records. In order to evaluate persistence with therapy, we identified time (months) in which each patient remained in therapy (follow up period) and therefore we divided injectable group and oral group into 5 subgroups based on the follow up period of the patients (6 months, 12 months, 24 months, 36 months and 48 months). We analysed data relating to the delivery of medicines to assess adherence to treatment and we defined "adherents to therapy" patients who had received at least 80% of the all therapy expected according to the dosage indicated in the Summary of Product Characteristics (SmPC) during the follow-up period.

Results The analysis included 136 patients (73 in injectable group and 63 in oral group). During the follow up period, patients who discontinue DMTs for switching or stopping therapy were 30 (41%) in the injectable group and 15 (24%) in the oral group. Reasons to therapy switch/suspension were onset of side effects, therapeutic ineffectiveness and in a few cases, it was a patient's independent choice. Evaluating medication persistence, in both groups we found a decreasing trend as the time in which patients remain on therapy increases. The first 6 months of therapy are decisive because we noticed a clear reduction of patients who remain in therapy with injectable DMTs. Adherence to treatment was almost high in patients of both injectable and oral group. In injectable group, 74% of patients were adherent to the prescribed therapy, while 94% of patients treated with oral DMTs were adherent to the therapy.

Conclusion The present analysis confirms the usefulness of oral drugs in the management of RRMS and the convenience for many patients of a more comfortable and less invasive route of administration which is reflected not only in adherence to therapy but also in greater medication persistence. The adverse reactions detected in our study underline an uncertain safety profile for these drugs and highlight the importance of monitoring the risks and benefits in real world.

Keywords: Multiple Sclerosis, Disease-Modifying Therapies, Real World Data, Therapy Switch, Medication Persistence, Adherence to Treatment.

Anticoagulant therapy: safety analysis use in patients in Tuscany region

Mariapaola Lisi, Maria Parrilli[1,2], Martina Del Lungo[2], Linda Giovannetti[1], Valentina Borsi[2]

Training held at
[1] Centro di Farmacovigilanza della Regione Toscana, Italy
[2] USL Toscana Centro, Italy

ABSTRACT

Background: The aims of pharmacovigilance are to enhance patients' care and safety and to provide reliable and balanced information for effective assessment of the risks and benefits of medical drugs. The anticoagulant therapy in patients is associated with risk of bleeding.

Aim: this study was to evaluate the frequency of spontaneous reports of bleeding in patients treated with DOACs compared to patients treated with warfarin.

Methods: We included all spontaneous reports of bleeding collected in the National Pharmacovigilance Database since January 1st, 2019 until December 31st, 2019 in which apixaban, dabigatran, edoxaban, rivaroxaban (direct-acting oral anticoagulants, DOACs), and warfarin were identified as suspected causative drugs and for which the data source was identified in a Tuscan Health District.

Results: The serious bleeding events in the gastrointestinal and nervous systems were major in both DOACs and warfarin treatment. In particular, in warfarin treatment the 100% of ADRs for Nervous system disorders and 58,5% for gastrointestinal disorders were serious; in DOACs treatment the 94,4% and 79,7% in Nervous system and gastrointestinal disorders, respectively, were serious. The incident rate calculated as ADR/DDD*10000 showed that warfarin was associated a minor safety of DOACs (16,19 versus 0,35) in general but also for bleeding events (11,68 versus 0,20) confirming a lower risk of bleeding of DOACs compared to warfarin.

Conclusion: In conclusion, in the Tuscan population, the DOACs were associated with a lower risk bleeding compared to warfarin.

Keywords: Direct-acting oral anticoagulants, Warfarin, Gastrointestinal bleeding, Nervous system bleeding.

Quality control process for adverse drug reaction processing

Chiara Mancini, Stefano Franchini

Training held at
Medical Affairs Consulting, Milano, Italy

ABSTRACT

Background: Health agencies have detailed requirements on how to set up and to ensure a quality system in Pharmacovigilance. In European Union, this is ruled by Regulations and Directive with focus on module VI revision 2 of the guidelines on GVP which came into force on 22 November 2017. The Quality Control (QC) procedure, carried out accurately and precisely, is essential for identifying and correcting errors during the insertion, for the analysis and management of the Individual Case Safety Reports (ICSRs) and therefore for the whole procedure.

Objective The purpose of this study was to evaluate the efficiency of the QC process and to verify the quality of the ICSRs received by Medical Affairs Consulting (MAC), a pharmaceutical consultancy agency.

Methods: Between December 2019 and January 2020, MAC received, on behalf of one of its Clients, ICSRs containing serious and non-serious adverse drug reactions (ADRs) from several countries. All reports have been entered in the company safety database. The analysis was carried out in accordance with the QC process, taking into account all information collected in each ICSRs and comparing this to source documentation received.

Results: During the study period, MAC received and included 30 total reports (serious and non-serious, initial and follow-up) in the database from EudraVigilance, spontaneous ICSRs and literature. As a result of the QC process a number of corrections to the information were observed, the majority of which were in the following fields: ADR, narrative and other comments.

Conclusions: This study has shown that a meticulous and precise QC is essential in identifying and correcting errors during data entry, analysis and management of ICSRs. It is imperative to have accurate and clear procedures to improve and increase the quality of Pharmacovigilance and ICSRs in order to obtain optimal management of medicinal product safety information.

Keywords: Good Pharmacovigilance Practices, European Union Drug Regulating Authorities Pharmacovigilance, Individual Case Safety Report, Medical Dictionary for Regulatory Activities Quality Control.

Analysis and monitoring of adverse intravitreal drugs reactions Avastin, Lucentis and Eylea: from EudraVigilance to RNF, from Piedmont reality to that of the ASL Città di Torino

Giulia Papotti[1], Paola Crosasso[1], Edoardo Pierobon[2]

Training held at
[1] Asl Città di Torino, S.C. Farmacia Ospedaliera del P.O. Maria Vittoria, Torino, Italy
[2] SSFO UNITO, ovvero Scuola di Specializzazione in Farmacia Ospedaliera, Università degli Studi di Torino

ABSTRACT

Background Age-related macular degeneration (AMD) and diabetic macular edema (DME) are the two main causes of progressive vision loss and blindness in developed countries (1). In Italy, about 800.000 to 1.000.000 patients show initial signs of senile maculopathy and an estimated 100.000 new cases per year, while the incidence of diabetic macular edema has dramatically increased in the last 40 years, affecting more than 60% of diabetics. Avastin®, Eylea® and Lucentis® are the drugs most commonly used in ophthalmological settings, in particular, the former is used, under law 648/96, to treat age-related macular degeneration and visual impairment for diabetic macular edema. Eylea® and Lucentis®, on the other hand, contain in SmPC these indications and have obtained the AIFA indication and the refundability of the National Health Service (NHS). All three drugs inhibit signalling mediated by VEGF, which is responsible for proliferation and neovascularization, albeit with three different mechanisms.

Aim The purpose of this work is to compare the safety data of these three drugs, which are collected from the registration studies with those collected during the pharmacovigilance phase.

METHODS Data from the National Network of AIFA, the European EudraVigilance Network and the WHO World Network were analysed. At the national level, in particular, we focused on the Piedmont reality of the ASL Città di Torino.

Results The WHO VigiBase database allows you to analyse suspected adverse reactions (ADRs) when the drugs have been put on the market, in particular for Eylea® there are 28.994 reports, most of these are related to the site and the methods of administration (30,1%). For Lucentis® 32.679 total reports were found, of which 27,2% involve the eye and 19,8% the administration site. The analysis of the European EudraVigilance database also allows to analyse data on the severity of ADRs: for Eylea® there are 10.592 reports, of which 96,3% are serious and only 3,7% not serious; for Lucentis® we found 19.030 and in a similar percentage to Eylea® in terms of severity (96,6% severe and 650 3,4% non-serious). In Italy, the analysis of reports for Avastin®, used off-label, records 73, of which 19 are serious (26%) and 54 non-serious (74%); for Eylea® a total of 58 reports were extracted, 52 of which were classified as serious (89,7%) and 6 as non-serious (10,3%); finally, for Lucentis® 84 total reports, of which 75 serious (89,3%) 9 non-serious (10,7%). Finally, we did not find any reports at the ASL Città di Torino.

Conclusions This analysis shows that intravitreal drugs are well tolerated and almost superimposed from a safety point of view: this is certainly a fact to be taken into account in the light of a reallocation of the scarce economic resources which the NHS now has to deal with. In the national context, the trend of pharmacovigilance signals is almost comparable to that of Europe and the World, although there are more signs regarding the cardiovascular area and regarding a presumed ineffectiveness of the drug; local ADRs are the most common and more monitoring and caution should be reserved for those with cardiovascular problems who are most exposed to severe ADRs.

Keywords: Intravitreal Treatments, Safety, Real-Life, Age-Related Macular Degeneration, Off-Label.

Therapeutic ineffectiveness and pharmacovigilance: a critical evaluation of the cases included in RNF regarding Lombardy in the year 2019

Debora Pensabene, Olivia Leoni

Training held at
Regional Center of Pharmacovigilance, Region of Lombardy, Milano, Italy

ASTRACT

Background: Therapeutic ineffectiveness is a frequent drug-related problem that can occur in a variety of different situations and that can be caused by different mechanisms, such as inappropriate use, interactions or metabolic abnormalities. Observations of unexpected ineffectiveness in patients can provide important information with regard to such situations. Therefore, ineffectiveness, especially if unexpected, is a potentially important reportable event in pharmacovigilance.

Objective: The aim of this project was to perform an analysis of reports of adverse drug reactions (ADRS) due to therapeutic ineffectiveness which arose in Lombardy during 2019, in order to identify criticalities in reporting and to identify the potential causes of therapeutic ineffectiveness.

Methods Lombardy reports regarding suspected adverse drug reactions (ADRs) due to drug ineffectiveness that were inserted in the National Pharmacovigilance Network (RNF) from January to December 2019 were checked and evaluated for data completeness and accuracy. The analysis was performed by using the VigiSegn application. In addition, each case was analysed using the algorithm proposed by Vaca González to identify the potential causes of therapeutic ineffectiveness

Results: Only in 21 cases, out of 349 reports the cause of ineffectiveness was described or reported as therapeutic drug errors. In the remaining reports the most common cause was identified as the disease progression in elderly patients with predisposed and concurrent conditions.

Conclusions: Spontaneous reporting of ineffectiveness may be of great importance in pharmacovigilance due to the fact that ineffectiveness may be an early warning in a variety of situations. However, an important objective must be to improve the quality of such reports and to stimulate the collection of data in support of the reported ineffectiveness.

Keywords: Terapeutic Ineffectiveness, National Pharmacovigilance, Network (RNF), ADR (Adverse Drug Reaction).

The role of medical information and pharmacovigilance team: the experience of an Italian affiliated pharmaceutical company

Vittoria Presotto, Matteo De Petris

Training held at
AstraZeneca SpA Basiglio, Milano, Italy

ABSTRACT

Background: The Medical Information (MI) service is a tool used by pharmaceutical companies to answer unsolicited requests associated with their products. During the past years in the United States, a consortium of pharmaceutical manufacturers known as Pharma Collaboration for Transparent Medical Information (phactMI), was created to harmonize MI processes and to improve the efficiency of medical responses across countries (1). Recently, in Europe, a similar group called the Medical Information Leaders Europe group (MILE), was created to develop additional principles and to answer health requests. Moreover, MILE suggested a collaboration between the MI team and the Pharmacovigilance team (PV), as the two groups together can provide complete safety information. Each Marketing Company provides MI services and decides how to apply MILE principles supporting the safe and effective use of medicines (2).

Aims: The main purpose of this project is to understand the role of the MI and PV teams within a marketing company analysing safety responses and AE reports created directly by the Italian Global Medical Information Platform (GMIP), where all MI requests and answers are collected.

Methods. Firstly, the download of the different requests and associated adverse events is carried out through GMIP, the platform used by the MI team. Secondly, the data are analyzed and processed using excel tables, working in line with local and global operating procedures.

Results: In 2019 MI team have collected 46 AEs and most of the requests have been made by consumers by telephone calls. All requests have been entered in the database on time and according to the procedures.

Conclusions: In this study, is underlined the importance of collaboration between MI and PV teams, which are responsible for responding safety questions, recognising and inserting correctly adverse events. The two teams work well together meeting the quality requirements.

Keywords: Medical Information, Pharmacovigilance, Safety Requests, AE Reports, Quality Requirements.

Artificial intelligence applied to pharmacovigilance: evaluation of critical issues in relation to real opportunities

Bianca Maria Salvatore, Marcella Falcone, Duccio Micela, Marco Giacomelli

Training held at
JSB Solutions Srl, Italy

ABSTRACT

Background: Pharmacovigilance (PhV) detects, assesses and prevents adverse events (AEs) and other drug-related problems by collecting, evaluating, and acting upon AEs. The volume of individual case safety reports (ICSRs) increases yearly. In this landscape, embracing assistive technologies at scale becomes necessary to obtain a higher yield of AEs, to maintain compliance, and transform the PhV professional work life. In accordance with current legislation, Marketing Authorisation Holders (MAHs) that have requested the authorization of a medicinal product have the obligation to monitor the safety profile of this product also by monitoring the data published in the literature. This is an activity that must be regulated within the MAH's PhV system and must be carried out on a weekly basis; therefore, a considerable use of resources and time is required for this process.

Aim: The thesis project focus on the application of artificial intelligence to a PhV process or the screening of medical-scientific literature. The aim of the project is to measure how much artificial intelligence can understand, evaluate and order the contents of scientific articles in order to identify an ICSR. It will be calculating the precision and accuracy with which the Artificial Intelligence (AI)processes the data and whether it is able to directly establish the relationship between adverse drug reaction (ADR) and drug.

Methods: The data used to train the cognitive service of IBM Watson Knowledge Studio were an annotated corpus consisting of 74 case reports from MedLine database (PUBMED). The model developed and validated was imported into IBM Watson Discovery and 151 new articles have been tested by query into a JSB Solutions Srl interface.

Results: By applying the model, on a total of 151 articles, after making the queries, a list of 79 articles have been shown. All the articles have been screened in order to verify if they were ICSR or studies. 71 were ICSRs where the correct substance and ADR were found, 8 were false positive.

Conclusion: As AI is introduced to pharmacovigilance, new skills and competencies are required, these competencies are not considered all-inclusive for the field of computer science but serve as an indication of what skills a professional should acquire to work with AI in pharmacovigilance. Drug safety officers should develop the ability to understand concepts of artificial intelligence, natural language processing, machine learning and deep learning; also, should work on how to interact with and identify issues with artificial intelligence.

Keywords: Pharmacovigilance, Individual case safety report, Artificial intelligence, IBM Watson, Query, Machine learning.