Chapter

Data Mining Strategy to Prevent Adverse Drug Events: The Cases of Rosiglitazone and COVID-19 Vaccines

Maria-Isabel Jimenez-Serrania

Abstract

This chapter analyzes how a simple strategy of early detection of safety signals using data mining can prevent the potential risk of adverse events with new or former drugs. We first present the case of an active antidiabetic ingredient, rosiglitazone. The capability of the strategy to detect the risk of heart failure among the data reported during the first 8 years of commercialization was demonstrated 2 years before rosiglitazone was withdrawn from the market in 2020 due to that risk. Ten years later, agility in obtaining safety signals after marketing a drug was put to the test with COVID-19 vaccines. Among adverse events notified during only 2 months of follow-up, we early detected thrombosis following COVID-19 vaccines. Several weeks after, these events were in the spotlight of the vaccination campaign and defined changes in the type of vaccine administered according to susceptible age groups. This early analysis strategy of suspected adverse drug reactions reported can provide useful information in making decisions in a faster way than the standard data mining methodology.

Keywords: data mining, early detection, adverse reaction, rosiglitazone, heart failure, COVID-19 vaccines

Keypoints:

- Heart failure signal related to rosiglitazone was detectable 2 years before the final withdrawal.
- Vaccine-induced immune thrombotic thrombocytopenia signals related to viral vector vaccines for COVID-19 were detectable only 2 months later than the beginning of vaccination campaigns.
- The strategy based on Bayesian Confidence Propagation Neural Network (BCPNN) extended to multiple comparison settings considering as a comparative database the Anatomical Therapeutic Chemical (ATC) group reports instead of all the database seems to be effective in the early detection of severe signals.

1. Introduction

We want to expose and analyze two different situations in the extent and duration of adverse drug reactions (ADRs) that lead to regulatory actions years after and the capability of a specific strategy to detect them on time.

The 'looking back' example is about rosiglitazone, an active ingredient only used for a restricted population, and we analyze cumulative data during 8 years since commercialization.

The 'looking at the present' example is about viral vector COVID-19 vaccines, worldwide used, and we analyze during only 2 months since commercialization.

First of all, we present the background situations.

1.1 Looking back: The case of rosiglitazone and cardiovascular risk

Rosiglitazone is an active ingredient used to treat type 2 diabetes. There has been much debate about the cardiovascular risks, particularly heart failure, associated with its use.

In the 2000s, several studies suggested that rosiglitazone may increase the risk of cardiovascular events such as heart attacks and strokes. For example, a meta-analysis published in 2007 in the *New England Journal of Medicine* found that rosiglitazone was associated with a significant increase in the risk of heart attacks, as well as an increased risk of death from cardiovascular causes [1]. Another meta-analysis found rosiglitazone was associated with a significant increase in the risk of myocardial infarction [2]. The same study found that rosiglitazone was associated with a nearly twofold increase in the risk of congestive heart failure [3].

However, other studies found no significant increase in cardiovascular risk with rosiglitazone. For example, a study published in 2009 in the Lancet found no significant difference in the risk of cardiovascular events between patients treated with rosiglitazone and those treated with other diabetes medications [4].

Rosiglitazone was withdrawn from the European market in 2010 due to its cardiovascular risk. The European Medicines Agency (EMA) implemented an immediate suspension of the drug, meaning that it was no longer available in Europe [5, 6]. The suspension of the marketing authorizations of rosiglitazone was recommended across the European Union by the European Committee on Medicinal Products for Human Use [6]. The withdrawal of rosiglitazone from clinical use was also recommended in the UK [6, 7]. The withdrawal of rosiglitazone-containing medicines was a result of a European wide review of available data on the risks and benefits of rosiglitazone.

Although the FDA has also warned that rosiglitazone causes or exacerbates congestive heart failure in some patients [8], some scientific uncertainty about the cardiovascular safety of rosiglitazone medicines remains. In light of the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, the concern is substantially reduced, and the rosiglitazone Risk Evaluation and Mitigation Strategy (REMS) program requirements will be modified [9].

1.2 Looking at the present: The case of COVID-19 vaccines and immune thrombotic thrombocytopenia (VITT)

The Regulatory Agency of the United Kingdom (Medicines and Healthcare Products Regulatory Agency, MHRA), followed by the United States (Food and Drug

Administration, FDA) and the European Union (European Medicines Agency, EMA), issued an emergency use authorization for the first COVID-19 vaccine over December 2020 [10–12].

The main difference between Conditional marketing authorization in Europe (or Emergency Use Authorization in the United States) – EUA – compared with full approval is the amount of data required by the Regulatory Agencies to grant approval. A EUA may be issued based on interim results from clinical trials, while a Biologics License requires completion of clinical trials.

For example, for a EUA for a COVID-19 vaccine, the FDA requires that at least half of the clinical trial participants be followed for at least 2 months after vaccination. For full FDA approval of a COVID-19 vaccine, participants are followed for at least 6 months.

The first COVID-19 vaccines were Pfizer-BioNTech (after Comirnaty) [13] and Moderna (after Spikevax) [14], both of which are mRNA vaccines. This vaccine contains mRNA that carries the surface glycoprotein S (spike) of the SARS-CoV-2 virus and is encapsulated in a lipid shell that helps stabilize the RNA and facilitate the entry of the vaccine into cells. To maintain stability of mRNA, these must be stored and transported in ultra-low temperature (ULT) conditions of −90°C to −60°C.

Both the Oxford-AstraZeneca (after Vaxzevria) [15] and Janssen (after JCOVDEN) [16] vaccines, as well as the Gam-COVID-Vac (after Sputnik V) vaccine [17] in Russia, are carrier- or vector-vaccines, which instruct human cells to make the SARS-CoV-2 spike protein. For this vaccine technology, scientists engineer a harmless, inactivated common adenovirus (which can cause colds and other illnesses when it is active) that carries genetic code -DNA- to a vaccine recipient's cells. The code then instructs the cells to produce a spike protein that trains the body's immune system, which then creates antibodies and memory cells to protect against an actual SARS-CoV-2 infection.

Viral vector vaccines for COVID-19 (Oxford-AstraZeneca's vaccine; Janssen-Johnson & Johnson; Sputnik V) are stronger than mRNA vaccines (Pfizer, Moderna). DNA is not as fragile as RNA, and the tough protein coat of the adenovirus helps protect the genetic material it contains. As a result, viral vector vaccines do not have to remain frozen. The vaccine is expected to last at least 6 months if refrigerated at 2–8°C.

Thrombosis, the formation of blood clots in blood vessels, has been observed in a small number of people who have received certain COVID-19 vaccines. This has led to concerns and investigations into the potential link between thrombosis and COVID-19 vaccines.

In late February 2021, a prothrombotic syndrome was observed in a few individuals who received the adenoviral vector-based vaccine. Subsequently, similar findings were observed in individuals who received the Janssen; Johnson & Johnson vaccine, also based on an adenoviral vector [18, 19].

The specific type of blood clot that has been observed in a small number of people who have received the AstraZeneca and Janssen COVID-19 vaccines is called cerebral venous sinus thrombosis (CVST). This type of blood clot occurs in the veins that drain blood from the brain and can lead to serious complications if not treated promptly. Additionally, CVST and thrombocytopenia together are called thrombosis-thrombocytopenia syndrome (TTS); and TTS associated with COVID-19 vaccination has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT) [20].

VITT is characterized by the presence of single or multiple thrombosis, mainly venous but also arterial, with a certain predilection for affecting unusual locations,

such as the splanchnic territory or the cerebral venous sinuses. The presence of anti-platelet factor 4 (anti-PF4) antibodies causes platelet aggregation and micro- and macrothrombosis, causing marked thrombocytopenia and the characteristic thrombotic manifestations of the syndrome. VITT has been associated with nonreplicating adenovirus vector vaccines [21].

To mitigate the risks associated with thrombosis and COVID-19 vaccines, health authorities and vaccine manufacturers closely monitored the situation and implemented measures such as age restrictions and enhanced warning labels [22]. Additionally, individuals who receive COVID-19 vaccines are aware of the symptoms of thrombosis, which can include severe headache, chest pain, leg swelling, and shortness of breath, and seek medical attention immediately if these symptoms occur.

It is important to note that the risk of developing thrombosis after receiving a COVID-19 vaccine appears to be much lower than the risk of developing thrombosis after contracting COVID-19 itself [23]. COVID-19 infection is associated with a higher risk of blood clots, and the benefits of vaccination in preventing COVID-19 and its serious complications far outweigh the risks.

2. Materials and methods

2.1 Methodological bases

First, it is important to review some actual definitions about adverse reactions and signals.

There is currently no unified definition for the term 'signal' in pharmacovigilance. According to the World Health Organization (WHO), a signal or alert is a 'notification of a possible causal relationship between an adverse event and a drug, previously unknown or incompletely documented' [24]; while according to the Pharmaceutical Research of Manufacturers of America-Food and Drug Administration (PhRMA-FDA) Collaborative Working Group on Safety Evaluation Tools, a signal is 'a relationship between a drug and an event that strong enough, using a predetermined threshold or analyst-defined set of criteria, to warrant further evaluation' [25].

The spontaneous notification systems in pharmacovigilance have large databases and are mainly focused on the early detection of adverse reactions of commercialized drugs with cumulative data over time [26].

In the past, this signal detection was based on a case-by-case analysis. In recent years, data mining techniques have become a more efficient method, understanding it as an analysis of data from different perspectives and the extraction of relevant information from them.

In the case of signal detection, these automated methods use algorithms to discover unexpected events within large and entire pharmacovigilance databases. These algorithms are based on analyzing how much the number of cases observed through notifications differs from the number of expected cases; that is, they calculate estimators of the disproportionality of notifications [27]. That is why, currently, in addition to the alerts generated in the Regional Pharmacovigilance Centers, active searches for signals can be carried out using these automated methods.

Since 1998, the Uppsala Monitoring Center belonging to the WHO has been using a specific Bayesian method as an automated system for signal detection from the WHO database of suspected adverse drug reactions [28].

It starts from the method called Bayesian Confidence Propagation Neural Network (BCPNN) based on that, for each individual notification in an ADR suspicion notification database, there is a probability that a specific reaction already is collected in that base, that is, the previous probability is available. If the reports of these cases contain a specific drug, the posterior probability will be obtained. If the posterior probability is greater than the prior probability, it means, on the one hand, that the presence of the drug in the notification increases the probability that the reaction will be present; and, on the other hand, that the drug-ADR pair is present in the database more frequently than expected [28, 29].

For more mathematical detail, the BCPNN model is based on the calculation of the called Information Component (IC) for each drug-ADR combination of the integral base [30].

This IC is the logarithmic measure of disproportionality used by the BCPNN method. It is defined mathematically by the equation: $IC = \log_2 (P_{XY} / P_X P_Y)$; where P_X is the probability of finding a certain drug in a notification; P_Y is the probability of finding a given adverse reaction in a notification; and P_{XY} is the probability of finding a drug-adverse reaction combination in a report [31]. The source of comparison is the entire database.

When calculated from a finite number of reports, it is really an estimate of the true value of IC. ADR-drug combinations with positive IC values represent the most frequently reported combinations than expected, while those with negative ICs represent the combinations reported less frequently than expected [31].

The BCPNN model adopts a Bayesian approach assuming a prior distribution centered around a relative risk of 1 ($RR_0 = 1$, interpreted as no relationship between drug and ADR), based on empirical evidence. The IC levels are, therefore, averages of the posterior distribution of the true relative risk [28, 29]. From the IC distribution obtained, the exact variance and standard deviation are calculated, the latter being the measure of CI robustness [32].

Once the IC is calculated, a signal is generated if the 2.5% quantile of the IC distribution is greater than 0 ($Q_{0.025}IC > 0$). The IC distribution initially approximated the normal distribution [28], and a more accurate model was subsequently proposed based on empirical evidence from the WHO database [29] and on extensions of Monte Carlo simulations [33].

It should be noted that the IC value only provides a quantitative indication of the correlation between a medication and an ADR. To establish a causal relationship between the latter, the strength of the clinical diagnosis must be estimated by studying individual reports or through controlled trials [34].

2.1.1 Extension to the multiple comparison setting

The original decision rules for the automatic generation of signals in pharmacovigilance include models such as BCPNN that are based on arbitrary limits; that is, there is no signal evaluation measure associated with the adopted decision rule.

Due to this aspect, the review carried out within the general Bayesian decision structure of the BCPNN model applied in pharmacovigilance has resulted in a new ordering procedure for drug-ADR pairs based on the posterior probability of the null hypothesis of interest [26]. The approach used makes it possible to obtain, indirectly, the Bayesian estimators for false positives (FDR) and for false negatives (FNR) that serve as an evaluation measure of the detected signals [35]. The key estimator is the calculated Bayesian false discovery rate (FDR) and the threshold to a positive signal fixed in FDR < 0.05. Bayesian estimators of sensitivity (Se) and specificity (Sp) are also considered useful [36].

These Bayesian methods have been shown to outperform other data mining methods that use the relationship between the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) as estimators of disproportionality [37]. Additionally, the capacity of the BCPNN method for the early detection of new adverse drug reactions (ADRs) has been widely demonstrated [26, 28, 30, 34, 38–41].

2.2 A strategy for early detection of safety signals

Obviously, adaptations of this methodology can be valuable and trustworthy with a correct interpretation of the signals [42]. The new strategy consists of contrasting all the ADR of a specific Anatomical Therapeutic Chemical (ATC) Classification System subgroup isolated from the integral database.

The algorithm was performed with the following arguments: the value of the relative risk (RR) proven to be higher than 1 (RR > 1 or RR > 2); minimum number of cases per pair [drug-adverse reaction] to be potentially considered as a signal (N = 1); rule of decision for the generation of signals: false discovery rate (FDR); limit or threshold for the decision rule: FDR > 0.05; statistics used for ordering the drug-ADR pairs: the posterior probability of the null hypothesis (post.H0); calculation of the distribution of the statistic of interest: by approximation to the normal distribution [28, 32] and using empirical estimation through Monte Carlo simulations (NB.MC = 10,000 or NB.MC = 50,000) [33]. The estimator of FDR < 0.05 and specificity (Sp) ≥ 0.99 are considered to interpret the results. Sensitivity (Se) values are typically low in the BCPNN approach [43], Se ≥0.20 is considered as a reference.

The estimator FDR assures that at least 95% of the signals detected are positive (only 5% of false positives). Moreover, if the estimator of false negatives (FNR) is 50% or lower, it implies that, at least, half of the signals rejected are effectively negative. In the results presented, all the FNRs were lower than 49%.

All signals were obtained and categorized according to the standard terminology, in essence, preferred terms (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) [44].

If we apply this strategy described to our cases of interest, algorithms were performed as followed.

2.3 Looking back: early detection strategy for rosiglitazone

- Study units: Spontaneous notifications of suspected adverse reactions associated with drug treatment of diabetes mellitus (Therapeutic Group A10 Drugs used in diabetes; ATC Classification) until 2008 in Spain. That year was selected as the final point for the analysis because it was 2 years before the suspension of commercialization of rosiglitazone in December 2010, to exclude from the analysis the possible over-reporting motivated by the results of the benefit-risk balance of the EMA published in 2008–2010 period.

- Data source: FEDRA® 2.0 database (Spanish Pharmacovigilance, Adverse Reaction Data), belonging to the Spanish Pharmacovigilance System of the Spanish Medicines Agency [45], which contains information on suspected Adverse Drug Reactions (ADR) detected and reported by health professionals and by pharmaceutical laboratories, after the start of marketing medicines and health products.

This information was requested from a Spanish Regional Pharmacovigilance Center (Valladolid) with prior permission from the Spanish Medicines Agency.

For the treatment of information on suspected ADRs, the 'Criteria for the use of data from the FEDRA Database of the Spanish Pharmacovigilance System' – SEFV/1/CT and the 'Rules for the correct interpretation and use of the data of the SEFV' – SEFV/2/CT.

2.4 Looking at the present: Early detection strategy for COVID-19 vaccines

- Study units: Spontaneous notifications of suspected adverse reactions associated with COVID-19 vaccines (Therapeutic Group J07BX Other viral vaccines: COVID-19 vaccines, Ebola vaccine, and smallpox vaccine; initially ATC assigned group) until the end of January 2021. That month was selected because it is 2 months before the first two cases of VITT were reported in patients who had received the AstraZeneca vaccine in Europe (March 7, 2021), specifically in Austria, and on March 14, 2021, the first case in Spain [21].

- Data source: free-user interface VigiAccess™ belonging to VigiBase®, the unique World Health Organization (WHO) global database for suspected ADRs maintained by the Uppsala Monitoring Centre (UMC) since 1968.

This database allows searching by active ingredient (not brand names) for all data coming from over 110 countries, undersigning a statement of the responsibility for the appropriate use and interpretation of data ('Important points to consider') [46]. It is not possible in VigiAccess to separate the numbers for specific vaccines.

This information was requested in the form of a free consultation. To access the search function, you must confirm that you have read and understood the statements for the treatment of information on suspected ADRs [47].

3. Results

3.1 Looking back for rosiglitazone

The only signals reported about heart failure appeared for the combination of active ingredient rosiglitazone o for the combination rosiglitazone plus metformin (see **Table 1**).

Active ingredient	Adverse drug reaction (Preferred term, PT)	N	$RR_0 > 1$ NB.MC = 10,000 FDR (<0.05)	$RR_0 > 2$ NB.MC = 10,000 FDR (<0.05)
Rosiglitazone+ metformin	Heart failure	6	0.000	0.008
Rosiglitazone	Heart failure	6	0.001	0.010

N (count), number of couples 'active ingredient-ADR' reported; RR_0, Relative Risk; NB.MC, Number of Monte Carlo simulations; and FDR, False Discovery Rate.

Table 1.
Heart failure, cardiovascular and related positive safety signals detected among notifications of antidiabetics in Spain, until 2008.

Due that data considered for this approach was until 2008, it is shown that the cardiovascular risk of rosiglitazone could have been detected 2 years in advance of its international alert and subsequent withdrawal in 2010.

No other cardiac risk was detected, but among vascular signals were peripheral edema by detemir and rosiglitazone plus metformin, edema by pioglitazone, and angioedema by rosiglitazone for RR > 1, for RR > 2, edema by rosiglitazone or by rosiglitazone plus metformin, and peripheral edema by pioglitazone were obtained.

Complete results for 'heart failure, cardiovascular, and related' signals during that period are reported in **Table A1** for RR0 > 1 and for RR0 > 2 in **Table A2**. It is relevant that signals appeared for relative risk RR0 > 1 and RR0 > 2 and without additional Montecarlo simulation than the referenced method.

3.2 Looking back for COVID-19 vaccines

If we consider the standard relative risk ($RR_0 > 1$) and Montecarlo simulations, we can only detect thrombotic events with the smallpox vaccine. It has more sense to increase Montecarlo simulations than relative risk because the data reported are only for 2 months without cumulative information. So, if considering the same relative risk ($RR_0 > 1$) and increasing the Montecarlo simulations, COVID-19 vaccines appear in the results with five different types of thrombotic events; meanwhile, smallpox vaccines are almost the same. And that these last ones are almost the same in both situations validates the consistency of the results for COVID-19 vaccines (see **Table 2**). It is especially interesting to the signal of CVST and other unusual thrombotic locations in pelvic veins.

If we consider data and study periods, it is shown that the risk of CVST could have been detected 2 months before its international alert and subsequent management.

Complete results for 'thrombosis, thrombocytopenia, and related' events are reported in **Table A3** (Montecarlo simulations = 10,000) and in **Table A4** (for Montecarlo simulations = 50,000).

Active ingredient (vaccine)	Adverse drug reaction (preferred term, PT)	N	$RR_0 > 1$ NB.MC = 10,000 FDR (<0.05)	$RR_0 > 1$ NB.MC = 50,000 FDR (<0.05)
Smallpox	Thrombosis	8	0.008	0.001
Smallpox	Thrombotic thrombocytopenic purpura	4	0.030	0.004
Smallpox	Thrombocytosis	3	—	0.006
Smallpox	Thrombocytopenia	7	0.031	0.009
COVID-19	Thrombophlebitis	2	—	0.021
COVID-19	Cerebral venous sinus thrombosis (CVST)	2	—	0.021
COVID-19	Thrombophlebitis superficial	1	—	0.039
COVID-19	Pelvic venous thrombosis	1	—	0.043
COVID-19	Venous thrombosis limb	1	—	0.047

N (count), number of couples 'active ingredient-ADR' reported; RR_0, Relative Risk; NB.MC, Number of Monte Carlo simulations; and FDR, False Discovery Rate.

Table 2.
Thrombosis, thrombocytopenia and related positive safety signals detected among notifications of COVID-19 vaccines in VigiAccess™, until the end of January 2021.

4. Discussion

4.1 Looking back: Positive signal of heart failure and rosiglitazone

This thiazolidinedione was marketed in 2001 and was exclusively indicated for combination with other antidiabetics in patients with diabetes mellitus type 2 in whom treatment with metformin or sulfonylureas is ineffective or contraindicated. It was presented with the potential advantage of having a better safety profile at the cardiac level [48] and was considered an active principle of 'eventual utility' (terminology indicating that the novelty brings some modest but real improvement, which may be useful in some eventual clinical situation) [49]. Subsequently, since 2007, rosiglitazone has been the subject of multiple safety information notes related to cardiac risk [50–52], the risk of fractures in women [53], and its benefit-risk ratio [54]. In 2008, it was once again warned of its cardiovascular risk [55].

The security warnings issued during its commercialization did not affect its offer of three presentations until its suspension in December 2010.

It is striking that, although no fatal cases due to heart failure related to rosiglitazone were reported in the study period, they were reported as severe cases.

Finally, in 2010, after more results were available on its benefit-risk relationship [56, 57], its commercialization was suspended [58–60]; specific recommendations were issued for patients receiving treatment with rosiglitazone so that, under medical supervision, they received an alternative treatment appropriate to their case [61, 62].

It is important to note the marketed fixed-dose combination of rosiglitazone, and related results obtained in this study. Since their commercialization began, both the combination of rosiglitazone and metformin (2005) and glimepiride-rosiglitazone (2007) have been classified as novelties that 'do not contribute anything new' [63] and 'do not represent a therapeutic advance' [64, 65], respectively. Both combinations could cause heart failure, among other adverse reactions, as we also obtained for rosiglitazone plus metformin, and the advantage of their use was limited to simplifying the treatment to facilitate therapeutic compliance.

Finally, and at the same time as rosiglitazone alone, in 2010, the marketing of rosiglitazone-metformin and glimepiride-rosiglitazone was suspended due to evidence of cardiovascular risk associated with rosiglitazone [51, 54–56, 58, 59].

Nowadays, the availability of rosiglitazone varies depending on the country and its health regulation. In the United States, for example, rosiglitazone is still available, but it can only be prescribed to patients who cannot control their diabetes with other medications and who have been informed about the associated cardiovascular risks. In Europe, some countries have allowed its use in special circumstances. In the United Kingdom, rosiglitazone can be prescribed in exceptional cases when other treatments are ineffective or contraindicated.

In other countries, such as Australia, Canada, and Japan, rosiglitazone is available, but its use has been recommended with caution due to the associated cardiovascular risks.

Ongoing research has been conducted to better understand the cardiovascular risks associated with rosiglitazone. A more recent systematic review and meta-analysis of the effects of rosiglitazone treatment on cardiovascular risk and mortality found that rosiglitazone is associated with an increased cardiovascular risk, especially for heart failure events [66]. This study also found that the strength of the evidence

varied, and effect estimates were attenuated when sources and analytical approaches were varied, and conclusions were corrected subsequently.

Another study found that rosiglitazone is associated with a significantly increased risk of heart failure, with little increased risk of myocardial infarction, without a significantly increased risk of stroke, cardiovascular mortality, and all-cause mortality compared with placebo or active controls [67].

It is important to note that information about the availability of rosiglitazone may change over time, so it is always advisable to consult with a healthcare professional or local regulatory authority for the most up-to-date information.

4.2 Looking at the present: Positive signal of thrombosis-thrombocytopenia syndrome associated with COVID-19 vaccination (VITT)

The most similar viral vector-based vaccines existing up to the same time of COVID-19 vaccines that time were smallpox and Ebola vaccines, in fact, the COVID-19 vaccines were first included in 2021 in the same J07BX group.

The signal of COVID-19 obtained more related to the actual VITT was cerebral venous sinus thrombosis (CVST). The smallpox vaccine also shows signals for thrombotic events and thrombocytopenia at a low or high number of simulations. This last result can act as a control because all COVID-19 signals only appear with a high number of simulations (see **Table 2**). It is in accordance with the limited data of spontaneous reports in the first month of world vaccination.

In essence, at the beginning of 2021, it would have been useful to monitor these types of ADRs related to vector-based vaccines to detect early signals with COVID-19 vaccines, as it appears with the results commented.

As previously mentioned, this CVST, after being renamed VITT, consists of a rare autoimmune response, more common in women under 60 years of age, which presents as thrombus formation in the cerebral sinus (intracranial) or in abdominal veins, associated with a low platelet count. It occurs between the third and twenty-first-day postvaccination. Some authors recommended close monitoring of at-risk patients, every 2–3 days, especially during the above-mentioned time interval of the first 15 days after vaccination [68].

COVID-19 itself also carries a high risk of thrombosis and coagulation abnormalities in hospitalized individuals [20]. However, it is important to note that the benefits of COVID-19 vaccination in preventing severe illness and death outweigh the risks of these rare adverse events.

In March 2021, countries in Europe and elsewhere put a pause on that vaccine after a handful of people – mostly women younger than 60 – also developed VITT. The European Medicines Agency (EMA) investigated the situation and concluded that these complications should be listed as very rare side effects of the AstraZeneca vaccine and said the benefits still outweighed the risks [69]. But several countries have restricted the use of the vaccine because of the clots.

Even though data of differentiated branded COVID vaccine cannot be extracted from VigiAccess™, it is striking that VITT cases only began to appear in March 2021 in Europe and not in the United States, where the AstraZeneca vaccine was not authorized at that time. In turn, 75% of the spontaneous reports as of January 25, 2021, had been notified from Europe and 25% from America.

So much so that, in the United States, a small number of serious blood clots has also been reported in people who -perhaps- received the AstraZeneca vaccine outside.

At that point, this observation and signals detected could lead to thinking that mRNA-based vaccines do not present the same risk as adenovirus-based vaccines of generating VITT. If the vaccination advanced almost parallelly in Europe and the United States, the difference in adverse reactions would be marked by the type of authorized vaccines.

4.3 Looking at our early signal detection strategy

Data mining can be very useful for detecting adverse drug reactions. With the increasing availability of electronic health records and other digital health data sources, data mining techniques can help to identify previously unknown or poorly understood ADRs by analyzing large datasets [70–72].

Overall, data mining can help to improve drug safety by detecting adverse reactions that may not have been identified through traditional methods, such as clinical trials or spontaneous reporting systems. These methods can help to detect patterns and relationships within the data that may not be immediately apparent, including potential associations between drugs and adverse events.

Traditional data mining algorithms can perform disproportionality analysis on spontaneous reporting system data to improve drug safety surveillance [71] but it requires access to huge and complete databases to perform the analysis.

This strategy apports agility and fewer requirements than extended database analysis. The approach generates the possibility of a sustainable follow-up for specific ATC groups of interest and short databases.

The strategy presented can be extended to other groups of active ingredients, which due to their mechanism of action or therapeutic approach, already present some associated risks, which allows the preliminary study of possible adverse reactions in new drugs that are being included in the same ATC group.

5. Limitations of the study

In the preliminary analyses, values of specificity and sensitivity of the BCPNN methodology, it is known are typically low [44]. Nonetheless, it is acceptable with very high specificity and low but conservative sensitivity.

VigiAccess™ only allows searching by active ingredient, and it implies the impossibility of separating the numbers for branded vaccines using this free database.

The extent list of other events reported in every case of study, and signals obtained, was not provided in this manuscript, but all algorithms were performed taking all of them into account.

6. Conclusions

The strategy of early signal detection of adverse drug reactions presented has been demonstrated that would have been useful to detect in the past the signal of rosiglitazone and cardiovascular risk, and also, in the present, for the signal of thrombosis-thrombocytopenia syndrome associated with COVID-19 vaccination.

The advantage of this data mining approach compared with the standard BCPNN based on IC, or other Bayesian methods based on a relationship between the Proportional Reporting Ratio (PRR) and the Reporting Odds Ratio (ROR) as

estimators of disproportionality, is the versatility shown using ATC group records from specific studies or from international databases and also validates it as a useful method for the early detection of ADRs. Its application could help to improve drug and vaccine safety and reduce health risks to patients.

Definitively, signals of ADRs would have to be more considered as a basis of study and regulatory risk-minimization actions in pharmacovigilance and reducing financial costs.

Acknowledgements

To the European University of Miguel de Cervantes (UEMC, Valladolid, Spain), for giving me time and permission to perform this study.

Conflict of interest

The author declares no conflict of interest.

A. Appendix

Active ingredient	Adverse drug reactions reported	N	Post. H0	FDR	FNR	Se	Sp
Rosiglitazone + metformin	Edema	11	0.000	0.000	0.639	0.009	1.000
Rosiglitazone	Edema	11	0.000	0.000	0.638	0.011	1.000
Pioglitazone	Peripheral edema	9	0.000	0.000	0.638	0.011	1.000
Rosiglitazone + metformin	Heart failure	6	0.002	0.000	0.636	0.019	1.000
Rosiglitazone	Heart failure	6	0.004	0.001	0.635	0.022	1.000
Pioglitazone	Edema	5	1.534	0.048	0.013	0.630	0.044
Rosiglitazone + metformin	Peripheral edema	4	0.087	0.029	0.626	0.062	0.997
Rosiglitazone	Angioedema	3	0.093	0.033	0.625	0.067	0.996
Detemir	Edema	3	0.108	0.043	0.623	0.078	0.994
Rosiglitazone	Peripheral edema	4	0.113	0.050	0.622	0.085	0.992

N (count), Number of couples 'active ingredient-ADR' reported; post.H0, Posterior probability of null hypothesis; FDR, False Discovery Rate; FNR, False Negative Rate; Se, Sensitivity; and Sp, Specificity.

Table A1.
Heart failure, cardiovascular and related positive safety signals detected among notifications of antidiabetics in Spain, until 2008, and with relative risk (RR)>1.

Active ingredient	Adverse drug reactions reported	N	Post. H0	FDR	FNR	Se	Sp
Rosiglitazone + Metformin	Edema	11	0.002	0.001	0.446	0.012	1.000
Rosiglitazone	Edema	11	0.004	0.001	0.445	0.015	1.000
Pioglitazone	Peripheral edema	9	0.005	0.001	0.445	0.016	1.000
Rosiglitazone + metformin	Heart failure	6	0.038	0.008	0.443	0.023	1.000
Rosiglitazone	Heart failure	6	0.050	0.010	0.443	0.024	1.000

N (count), Number of couples 'active ingredient-ADR' reported; post.H0, posterior probability of null hypothesis; FDR, False Discovery Rate; FNR, False Negative Rate; Se, Sensitivity; and Sp, Specificity.

Table A2.
Heart failure, cardiovascular and related positive safety signals detected among notifications of antidiabetics in Spain, until 2008, and with relative risk (RR)>2.

Active ingredient (vaccine)	Adverse drug reactions reported	N	Post. H0	FDR	FNR	Se	Sp
Smallpox	Thrombosis	8	0.044	0.008	0.457	0.176	0.999
Smallpox	Thrombotic thrombocytopenic purpura	4	0.127	0.030	0.437	0.245	0.992
Smallpox	Thrombocytopenia	7	0.141	0.031	0.437	0.247	0.992

N (count), Number of couples 'active ingredient-ADR' reported; post.H0, posterior probability of null hypothesis; FDR, False Discovery Rate; FNR, False Negative Rate; Se, Sensitivity; and Sp, Specificity.

Table A3.
Thrombosis, thrombocytopenia and related positive safety signals detected among notifications of COVID-19 vaccines in VigiAccess™, until the end of January 2021, and with relative risk (RR)>1.

Active ingredient (vaccine)	Adverse drug reactions reported	N	Post. H0	FDR	FNR	Se	Sp
Smallpox	Thrombosis	8	0.005	0.001	0.631	0.205	1000
Smallpox	Thrombotic thrombocytopenic purpura	4	0.019	0.004	0.607	0.281	0.998
Smallpox	Thrombocytosis	3	0.031	0.006	0.598	0.310	0.996
Smallpox	Thrombocytopenia	7	0.050	0.009	0.586	0.345	0.993
COVID-19	Thrombophlebitis	2	0.079	0.021	0.546	0.452	0.979
COVID-19	Cerebral venous sinus thrombosis (CVST)	2	0.079	0.021	0.544	0.457	0.979
COVID-19	Thrombophlebitis superficial	1	0.132	0.039	0.493	0.570	0.951

Active ingredient (vaccine)	Adverse drug reactions reported	N	Post. H0	FDR	FNR	Se	Sp
COVID-19	Pelvic venous thrombosis	1	0.133	0.043	0.480	0.594	0.943
COVID-19	Venous thrombosis limb	1	0.133	0.047	0.468	0.616	0.935

N (count), Number of couples 'active ingredient-ADR' reported; post.H0, posterior probability of null hypothesis; FDR, False Discovery Rate; FNR, False Negative Rate; Se, Sensitivity; and Sp, Specificity.

Table A4.
Thrombosis, thrombocytopenia and related positive safety signals detected among notifications of COVID-19 vaccines in VigiAccess™, until the end of January 2021, and with relative risk (RR)>1 and Monte Carlo simulations NB.MC = 50,000.

Author details

Maria-Isabel Jimenez-Serrania
ADViSE Group, Department of Health Science, Miguel de Cervantes European University (UEMC), Valladolid, Spain

*Address all correspondence to: ijimenez@uemc.es

References

[1] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine. 2007;**356**(24):2457-2471. DOI: 10.1056/NEJMoa072761

[2] Kaul S, Diamond GA. Rosiglitazone and cardiovascular risk. Current Atherosclerosis Reports. 2008;**10**(5):398-404. DOI: 10.1007/s11883-008-0062-7

[3] Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione drugs and cardiovascular risks: A science advisory from the American Heart Association and American College of Cardiology Foundation. Circulation. 2010;**121**(16):1868-1877. DOI: 10.1161/CIR.0b013e3181d34114

[4] Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. Lancet. 2009;**373**(9681):2125-2135. DOI: 10.1016/S0140-6736(09)60953-3

[5] Cheung BM. Behind the rosiglitazone controversy. Expert Review of Clinical Pharmacology. 2010;**3**(6):723-725. DOI: 10.1586/ecp.10.126

[6] Medicines and Healthcare products Regulatory Agency. Rosiglitazone: recommended withdrawal from clinical use [Internet]. 2010. Available from: www.gov.uk/drug-safety-update/rosiglitazone-recommended-withdrawal-from-clinical-use [Accessed: February 23, 2023]

[7] National Prescribing Centre (NPC). NPC Archive Item: Rosiglitazone: withdrawal from clinical use [Internet]. 2010. Available from: www.centreformedicinesoptimisation.co.uk/rosiglitazone-withdrawal-from-clinical-use/ [Accessed: February 23, 2023]

[8] Food and Drug Administration. FDA Drug Safety Communication: Ongoing review of Avandia (rosiglitazone) and cardiovascular safety [Internet]. 2010. Available from: www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-ongoing-review-avandia-rosiglitazone-and-cardiovascular-safety [Accessed: February 23, 2023]

[9] Food and Drug Administration. FDA Drug Safety Communication: Ongoing review of Avandia (rosiglitazone) and cardiovascular safety. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines [Internet]. 2013. Available from: www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-removal-some-prescribing-and-dispensing-restrictions [Accessed: February 23, 2023]

[10] Medicines and Healthcare products Regulatory Agency (MHRA). Regulatory approval of Pfizer/BioNTech vaccine for COVID-19. [Internet]. 2020. Available from: www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19 [Accessed: May 3, 2023]

[11] U.S. Department of Health and Human Services. COVID-19 Vaccine Milestones. [Internet]. 2023. Available from: www.hhs.gov/coronavirus/

covid-19-vaccines/index.html. [Accessed: May 3, 2023]

[12] European Medicines Agency. COVID-19 vaccines: Authorised. [Internet]. 2023. Available from: www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised [Accessed: May 3, 2023]

[13] Committee for Medicinal Products for Human Use (CHMP). Comirnaty. Annex I. Summary of product characteristics [Internet]. 2021. Available from: https://www.ema.europa.eu/documents/product-information/comirnaty-epar-product-information_en.pdf [Accessed: October 17, 2022]

[14] Committee for Medicinal Products for Human Use (CHMP). Spikevax. Annex I. Summary of product characteristics [Internet]. 2021. Available from: https://www.ema.europa.eu/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf [Accessed: October 17, 2022]

[15] Committee for Medicinal Products for Human Use (CHMP). Vaxzevria. Annex I. Summary of product characteristics [Internet]. 2021. Available from: https://www.ema.europa.eu/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf [Accessed: October 17, 2022]

[16] Committee for Medicinal Products for Human Use (CHMP). Jcovden. Annex I. Summary of product characteristics [Internet]. 2021. Available from: https://www.ema.europa.eu/documents/product-information/jcovden-previously-covid-19-vaccine-janssen-epar-product-information_en.pdf [Accessed: October 17, 2022]

[17] Central Drugs Standard Control Organisation (CDSCO). Sputnik V. Summary of product characteristics [Internet]. 2021. Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadSmPC/SMPCsputinikdr.Reddys.pdf [Accessed: October 17, 2022]

[18] Medicines and Healthcare products Regulatory Agency (MHRA). Yellow Card. COVID-19 Vaccine AstraZeneca. [Internet]. 2021. Available from: https://yellowcard.mhra.gov.uk/idaps/CHADOX1%20NCOV-19 [Accessed: May 1, 2023]

[19] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, EichingerS.Thromboticthrombocytopenia after ChAdOx1 nCov-19 vaccination. The New England Journal of Medicine. 2021;**384**(22):2092-2101. DOI: 10.1056/NEJMoa2104840

[20] Warkentin TE, Cuker A. COVID-19: vaccine-induced immune thrombotic thrombocytopenia (VITT) [Internet]. 2023. Available from: www.uptodate.com/contents/covid-19-vaccine-induced-immune-thrombotic-thrombocytopenia-vitt [Accessed: May 3, 2023]

[21] García-Azorín D, Lázaro E, Ezpeleta D, et al. Thrombosis with Thrombocytopenia Syndrome following adenovirus vector-based vaccines to prevent COVID-19: Epidemiology and clinical presentation in Spain. Neurologia. 2022. DOI: 10.1016/j.nrl.2022.04.010 [Online ahead of print]

[22] World Health Organization (WHO). Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease

(COVID-19). [Internet]. 2021. Available from: apps.who.int/iris/bitstream/handle/10665/342999/WHO-2019-nCoV-TTS-2021.1-eng.pdf?sequence=1&isAllowed=y [Accessed: May 1, 2023]

[23] European Medicines Agency (EMA). COVID-19 vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. [Internet]. 2021. Available from: www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots#:~:text=COVID%2D19%20Vaccine%20AstraZeneca%20is-,blood%20to%20clot)%20after%20vaccination [Accessed: May 1, 2023]

[24] Lindquist M, Edwards IR, Bate A, et al. From association to alert: A revised approach to international signal analysis. Pharmacoepidemiology and Drug Safety. 1999;**8**(Suppl 1):S15-S25. DOI: 10.1002/(sici)1099-1557(199904)8:1+3.3.co;2-2

[25] Almenoff J, Tonning JM, Gould AL, et al. Perspectives on the use of data mining in pharmaco-vigilance. Drug Safety. 2005;**28**:981-1007. DOI: 10.2165/00002018-200528110-00002

[26] Ahmed I, Haramburu F, Fourrier-Reglat A, et al. Bayesian pharmacovigilance signal detection methods revisited in a multiple comparison setting. Statistics in Medicine. 2009;**28**:1774-1792. DOI: 10.1002/sim.3586

[27] Figueiras A, editor. New Era in Drug Safety: A Challenge for Public Health. Santiago de Compostela: Táktika Comunicación; 2009

[28] Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. European Journal of Clinical Pharmacology. 1998;**54**:315-321. DOI: 10.1007/s002280050466

[29] Nóren GN, Bate A, Orre R, et al. Extending the methods used to screen the WHO drug safety database towards analysis of complex associations and improved accuracy for rare events. Statistics in Medicine. 2006;**25**:3740-3757. DOI: 10.1002/sim.2473

[30] Bate A, Lindquist M, Orre R, et al. Data-mining analyses of pharmacovigilance signals in relation to relevant comparison drugs. European Journal of Clinical Pharmacology. 2002;**58**:483-490. DOI: 10.1007/s00228-002-0484-z

[31] Rodríguez JL. Data mining in the WHO database. Knowledge detection. Information Centers for Medicines and Pharmacovigilance. 2023. Available from: evirtual.uaslp.mx/FCQ/farmaciahospitalaria/Paginas/modulo5.aspx [Accessed: April 4, 2023]

[32] Gould AL. Practical pharmacovigilance analysis strategies. Pharmacoepidemiology and Drug Safety. 2003;**12**(7):559-574. DOI: 10.1002/pds.771

[33] Nóren N, editor. A Monte Carlo Method for Bayesian Dependency Derivation. Gothenburg: Chalmers University of Technology; 2002

[34] Bate A, Lindquist M, Edwards IR. The application of knowledge discovery in databases to post-marketing drug safety: Example of the WHO database. Fundamental & Clinical Pharmacology. 2008;**22**(2):127-140. DOI: 10.1111/j.1472-8206.2007.00552.x

[35] Müller P, Parmigiani G, Robert C, et al. Optimal sample size

for multiple testing: The case of gene expression microarrays. Journal of the American Statistical Association. 2004;**99**:990-1001. DOI: 10.1198/016214504000001646

[36] McLachlan GJ, Bean RW, Jones LB. A simple implementation of a normal mixture approach to differential gene expression in multiclass microarrays. Bioinformatics. 2006;**22**:1608-1615. DOI: 10.1093/bioinformatics/btl148

[37] Roux E, Thiessard F, Fourrier A, et al. Evaluation of statistical association measures for the automatic signal generation in pharmacovigilance. IEEE Transactions on Information Technology in Biomedicine. 2005;**9**:518-527. DOI: 10.1109/titb.2005.855566a

[38] Bate A. Bayesian confidence propagation neural network. Drug Safety. 2007;**30**:62. DOI: 10.2165/00002018-200730070-00011

[39] Zorych I, Madigan D, Ryan P, et al. Disproportionality methods for pharmacovigilance in longitudinal observational databases. Statistical Methods in Medical Research. 2013;**22**(1):39-56. DOI: 10.1177/0962280211403602

[40] Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety. 2009;**18**:427-436. DOI: 10.1002/pds.1742

[41] Lindquist M, Stahl M, Bate A, et al. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. Drug Safety. 2000;**23**:533-542. DOI: 10.2165/00002018-200023060-00004

[42] Norén GN, Edwards IR. Modern methods of pharmacovigilance: Detecting adverse effects of drugs. Clinical Medicine (London, England). 2009;**9**(5):486-489. DOI: 10.7861/clinmedicine.9-5-486

[43] Tada K, Maruo K, Isogawa N, Yamaguchi Y, Gosho M. Borrowing external information to improve Bayesian confidence propagation neural network. European Journal of Clinical Pharmacology. 2020;**76**(9):1311-1319. DOI: 10.1007/s00228-020-02909-w

[44] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA Hierarchy. In: Medical Dictionary for Regulatory Activities [Internet]. 2018. Available from: www.meddra.org/how-to-use/basics/hierarchy [Accessed: March 26, 2023]

[45] Spanish System of Pharmacovigilance of Medicines for Human Use. FEDRA database (Spanish Pharmacovigilance, Adverse Reaction Data) 2000-2008. Spanish Medicines Agency. [Internet]. 2008. Available from: www.aemps.gob.es/medicamentos-de-uso-humano/farmacovigilancia-de-medicamentos-de-uso-humano/informacion-sobre-el-acceso-a-los-datos-de-fedra/ [Accessed: March 26, 2023]

[46] Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. VigiBase® [Internet]. 2019. Available from: www.who-umc.org/vigibase/vigibase [Accessed: April 21, 2023]

[47] Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. VigiAccessTM [Internet]. 2023. Available from: https://www.vigiaccess.org/ [Accessed: February 15, 2023]

[48] Cuesta MT, Martínez M. New active principles. Rosiglitazone. Inf Ter Sis Nac Salud. 2001;**25**:112-113

[49] CADIME, EASP. [Rosiglitazone (DCI)]. Ficha de novedad terapéutica. 2001;1-2

[50] European Medicines Agency (EMEA). EMEA statement on recent publication on cardiac safety of rosiglitazone (Avandia, Avandamet, Avaglim). Press release. [Internet]. 2009. Available from: www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf [Accessed: February 13, 2023]

[51] Spanish Agency for Medicines and Health Products. Informative note 2007/08. [Cardiac risk associated with rosiglitazone: Communication from the AEMPS on the recently published data] [Internet]. 2007. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2007/docs/NI_2007-08_rosiglitazona.pdf [Accessed: February 13, 2023]

[52] Ministerio de Sanidad PSeI. [Rosiglitazone: Cardiac risk] (ref.:2007/08, mayo). Inf Ter Sis Nac Salud. 2007;**31**:101-102

[53] General Subdirectorate of Medicines for Human Use – Spanish Agency of Medicines and Health Products. Informative note 2007/05. [Rosiglitazone and pioglitazone: increased risk of fractures in women] [Internet]. 2007. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2007/docs/NI_2007-05_rosiglitazona.pdf [Accessed: March 8, 2023]

[54] General Subdirectorate of Medicines for Human Use – Spanish Agency of Medicines and Health Products. Informative note 2007/13. [Pioglitazone and rosiglitazone: Conclusions from the evaluation of the benefit-risk balance in Europe] [Internet]. 2007. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2007/docs/NI_2007-13_glitazonas.pdf [Accessed: March 8, 2023]

[55] General Subdirectorate of Medicines for Human Use – Spanish Agency of Medicines and Health Products. Informative note 2008/02. [Rosiglitazone and cardiovascular risk: New contraindications and restrictions of use] [Internet]. 2008. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2008/docs/NI_2008-02_rosiglitazona.pdf [Accessed: March 8, 2023]

[56] General Subdirectorate of Medicines for Human Use – Spanish Agency of Medicines and Health Products. Informative note 2010/08. [Information on the benefit-risk assessment of rosiglitazone] [Internet]. 2010. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/docs/NI_2010-08_rosiglitazona.pdf [Accessed: March 8, 2023]

[57] Spanish Ministry of Health PSeI. Rosiglitazone: information on the benefit-risk balance (ref.: 2010/08, July). Inf Ter Sis Nac Salud. 2010;**34**:131

[58] Spanish Agency for Medicines and Health Products. Informative note 2010/12. [Rosiglitazone (Avandia®, Avaglim®, Avandamet®): marketing suspensión] [Internet]. 2010. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/docs/

NI_2010-12_rosiglitazona.pdf [Accessed: March 8, 2023]

[59] Spanish Agency for Medicines and Health Products. Informative note 2010/18. [Rosiglitazone (Avandia®, Avaglim®, Avandamet®): Marketing suspension on December 29. Information for healthcare professionals] [Internet]. 2010. Available form: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2010/docs/NI_2010-18_rosiglitazona.pdf [Accessed: March 8, 2023]

[60] Spanish Ministry of Health PSeI. Rosiglitazone: Marketing suspension (ref: 2010/12 and 18, September and December). Inf Ter Sis Nac Salud. 2011;**35**:67

[61] Spanish Agency for Medicines and Health Products. Informative note 2010/05. [Rosiglitazone (Avandia®, Avaglim®, Avandamet®): marketing suspension. Information for patients on drug safety] [Internet]. 2010. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/ciudadanos/2010/docs/NIP_2010-05_rosiglitazona.pdf [Accessed: March 8, 2023]

[62] Spanish Agency for Medicines and Health Products. Informative note 2010/06. [Rosiglitazone (Avandia®, Avaglim®, Avandamet®): marketing suspension on December 29. Information for patients on drug safety] [Internet]. 2010. Available from: www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/ciudadanos/2010/docs/NIP_2010-06_rosiglitazona.pdf [Accessed: March 8, 2023]

[63] CADIME, EASP. Rosiglitazone (DCI)/Metformin (DCI). Ficha de novedad terapéutica. 2005;**2005**:1-2

[64] CADIME, EASP. Glimepiride (DCI)/Rosiglitazone (DCI). Ficha de novedad terapéutica. 2008;**2008**:1-2

[65] CADIME, EASP. Pioglitazone (DCI)/Metformin (DCI). Ficha de novedad terapéutica. 2009;**2009**:1-2

[66] Wallach JD, Wang K, Zhang AD, et al. Updating insights into rosiglitazone and cardiovascular risk through shared data: Individual patient and summary level meta-analyses. BMJ. 2020;**368**:l7078. DOI: 10.1136/bmj.l7078

[67] Cheng D, Gao H, Li W. Long-term risk of rosiglitazone on cardiovascular events – A systematic review and meta-analysis. Endokrynologia Polska. 2018;**69**(4):381-394. DOI: 10.5603/EP.a2018.0036

[68] Bilotta C, Perrone G, Adelfio V, et al. COVID-19 vaccine-related thrombosis: A systematic review and exploratory analysis. Frontiers in Immunology. 2021;**12**:729251. DOI: 10.3389/fimmu.2021.729251

[69] European Medicines Agency. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. [Internet]. 2021. Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood [Accessed: February 15, 2023]

[70] Bone A, Houck K. The benefits of data mining. Elife. 2017;**6**:e30280. DOI: 10.7554/eLife.30280

[71] Hauben M, Horn S, Reich L. Potential use of data-mining algorithms for the detection of 'surprise' adverse drug reactions. Drug Safety. 2007;**30**(2):143-155. DOI: 10.2165/00002018-200730020-00004

[72] Guan Y, Qi Y, Zheng L, et al. Data mining techniques for detecting signals of adverse drug reaction of cardiac therapy drugs based on Jinan adverse event reporting system database: A retrospective study. BMJ Open. 2023;**13**(1):e068127. DOI: 10.1136/bmjopen-2022-068127