ORIGINAL RESEARCH ARTICLE

Drug Saf 2012; 35 (4): 315-323
0114-5916/12/0004-0315/$49.95/0

Cardiovascular, Ocular and Bone Adverse Reactions Associated with Thiazolidinediones

A Disproportionality Analysis of the US FDA Adverse Event Reporting System Database

Domenico Motola,[1] *Carlo Piccinni*,[1] *Chiara Biagi*,[1] *Emanuel Raschi*,[1] *Anna Marra*,[2] *Giulio Marchesini*[3] and *Elisabetta Poluzzi*[1]

1 Department of Pharmacology, University of Bologna, Bologna, Italy
2 Pharmacy Service, University Hospital of Ferrara, Ferrara, Italy
3 Metabolic Diseases & Clinical Dietetics, Department of Clinical Medicine, University of Bologna, Bologna, Italy

Abstract

Background: The risk of myocardial infarction, macular oedema and bone fractures associated with thiazolidinediones (TZDs) has been extensively investigated.
Objective: The aim of the study was to verify if the analysis of a large spontaneous reporting database could generate early signals on these adverse drug reactions (ADRs) associated with TZDs.
Methods: A case/non-case study, restricted to antidiabetic drugs, was performed on spontaneous reports of ADRs (2005–2008) in the US FDA Adverse Event Reporting System (AERS). The method was applied to TZDs, both as a drug class and as single agents. The reporting odds ratio (ROR) with 95% CI was calculated as a measure of disproportionality in the whole dataset and in a quarter-by-quarter analysis.
Results: TZD use was registered in 49 589 out of 301 950 drug-reaction pairs (16%), with significant disproportionality for myocardial infarction (ROR 4.71; 95% CI 4.40, 5.05), macular oedema (3.88; 2.79, 5.39) and bone fractures (1.73; 1.53, 1.96). Separate analysis of the two TZDs showed that only rosiglitazone was associated with myocardial infarction (7.86; 7.34, 8.34) and macular oedema (5.55; 3.94, 7.79), whereas pioglitazone was associated with multiple site fractures (2.00; 1.70, 2.35), in particular upper and lower limb and pelvic fractures. The quarter-by-quarter analysis identified disproportionality for myocardial infarction (3.13; 2.38, 4.10) and bone fractures since January–March 2005 (2.70; 1.04, 2.78).
Conclusions: The frequency of reporting of myocardial infarction, macular oedema and fractures was significantly higher for TZDs in comparison with other antidiabetic drugs, with large intraclass differences. Both myocardial

infarction and bone fracture signals appeared before major publications on these safety issues.

Background

Thiazolidinediones (TZDs), rosiglitazone and pioglitazone, are widely used drugs, alone or in combination with other glucose-lowering agents, in the treatment of type 2 diabetes mellitus. TZDs are agonists for peroxisome proliferator-activated receptor-γ (PPAR-γ), which are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose mainly by increasing insulin sensitivity in peripheral tissues. In the last few years, several warnings on their safety profile have been raised, concerning, in particular, a higher cardiovascular risk for rosiglitazone compared with placebo or older antidiabetic drugs and a higher risk of bone fractures both in men and women, in particular for pioglitazone. The first systematic evidence for the cardiovascular risk of rosiglitazone was published by Nissen and Wolski[1] in June 2007. On the basis of a large meta-analysis, the authors concluded that rosiglitazone increased the risk of myocardial infarction by about 40% compared with placebo; this risk was confirmed by further meta-analyses by Singh et al.,[2] who also found that the risk of heart failure was more than doubled, and by an update of the meta-analysis by Nissen and Wolski.[3] On the contrary, an association with a significantly lower risk of death, myocardial infarction or stroke was found for pioglitazone use among patients with diabetes,[4] but a recent observational study using medical records and administrative data did not detect any difference in cardiovascular outcomes between the two TZDs.[5]

A lot of evidence is also available on the risk of TZD-associated multiple site fractures both in women and men.[6,7] A case-control analysis published in 2009 showed that this risk exists for both drugs,[8] with a recent retrospective cohort study confirming this risk for women but not for men.[9] As to the risk of macular oedema, a role of TZDs as a definite cause of its exacerbation in diabetic patients is based on an exhaustive literature review.[10]

All these warning data on the safety profile of TZDs affect their benefit-risk ratio, in particular for rosiglitazone, and have raised the debate as to whether these drugs should be on the market or should be withdrawn. Both the US FDA and the European Medicines Agency (EMA) took action, restricting rosiglitazone use or withdrawing it from the market, respectively.[11,12]

The aim of our study was to verify if the quantitative analysis of large spontaneous reporting databases, such as the FDA Adverse Event Reporting System (AERS), could have generated early signals on the risks associated with TZD use. To this purpose, myocardial infarction, macular oedema and bone fractures were selected as examples of already known TZD-associated reactions that arose only several years after marketing approval.

Methods

The AERS is a computerized information database designed to support the FDA postmarketing safety surveillance programme for all approved drugs and therapeutic biological products. Healthcare professionals and consumers send reports voluntarily through the MedWatch programme or to manufacturers who are required to send these reports to the FDA as specified by regulations.[13] The AERS also includes serious and unlabelled spontaneous reports from non-US sources, sent mainly by the national/international Regulatory Agencies for collaborative purposes. The FDA staff code all reported adverse events using standardized international terminology, the Medical Dictionary for Regulatory Activities (MedDRA®),[14] and use reports from the AERS in conducting postmarketing drug surveillance and compliance activities and in responding to outside requests for information.

The raw data of the AERS database can be freely downloaded from the FDA website,[15]

starting from 2004, but their quality and completeness improved in 2005.

In the present study, we analysed the reports of the 4-year period January 2005–December 2008, during which warnings were issued on TZD use. For each 3-month period, tables including drug/biological information for as many medications as were reported for the event (DRUG file) and adverse events coded by MedDRA® terms (REACTION file) were retrieved. A unique number for identifying AERS reports allows the ability to link all the information from the different tables.

The Anatomical Therapeutic Chemical (ATC) code was used to identify TZDs and other antidiabetic drugs under investigation.[16] In order to collect all AERS reports containing antidiabetic drugs, a drug name archive including all generic and trade names of drugs marketed in the US and in most European countries was created by using public lists freely available on authoritative websites.[17,18] To compare ADRs reported for TZDs with those for other antidiabetics, we performed the analysis in terms of drug-reaction pairs. Therefore, reports concerning the combinations of different antidiabetics were split into different reports, depending on the number of active substances. An automated multistep process was applied to detect and exclude as many duplicates as possible in the database. It was performed using a record-linkage strategy, which groups records overlapping in four key fields: event date, patient's age and sex, and reporter country. Records with three overlaps and just one missing datum were considered as duplicates.

The association between drugs and ADRs was analysed by using a case/non-case method.[19,20] Cases were represented by the reports of ADR in which TZDs were the suspected drug for each level of MedDRA® hierarchy; non-cases were all the reports of the same reactions induced by drugs different from TZDs. The association between TZDs and ADRs were calculated by using the ADR reporting odds ratio (ROR) as a measure of disproportionality. The ROR compares the case/non-case ratio for a drug with the corresponding ratio for all other drugs.[21-23] A significant disproportionality was formally defined when the lower limit of 95% CI was >1. To this purpose, the statistical package Epi Info™, version 3.4.3-2007, was used.[24]

Safety data for TZDs were compared against other antidiabetic drugs. The method was applied to TZDs as a drug class but also as single agents, and for the specific ADRs compared with those observed with the use of other glucose-lowering agents. The ROR analysis was firstly performed for each System Organ Class (SOC), then for High-Level Classes (High-Level Group Term [HLGT] and High-Level Term [HLT]) and Preferred Terms (PT) related to the predefined ADRs of TZDs: myocardial infarction, bone fractures and macular oedema.

We also analysed the ROR quarter-by-quarter trend in order to describe the spontaneous reporting behaviour before, during and after the main publications on the safety concerns of these drugs.

Results

From 2005 to 2008, 77 669 reports concerning antidiabetic drugs were reported to the FDA AERS, corresponding to 301 950 drug-reaction pairs, with 49 589 pairs concerning TZDs. Biguanides were the class most frequently reported (26% of all antidiabetic ADR reports), followed by sulfonylureas (22%), exenatide (18%) and TZDs (16%). Among TZD-reported ADRs, rosiglitazone and pioglitazone accounted for 56% and 44% of cases, respectively. In 8045 reports out of 12 469 (65%), TZDs were co-suspected with other antidiabetic drugs. Figure 1 shows the quarterly trend in reporting frequency; almost all classes were characterized by a peak in the first quarter 2006, followed by a continuous decrease, particularly for exenatide (a reduction of 96% through the fourth quarter 2008).

According to the SOC level of the MedDRA® terminology, the most frequently reported SOCs for TZDs were 'investigations' (n = 8553), 'general disorders' (n = 7471), 'gastrointestinal disorders' (n = 6347) and 'cardiac disorders' (n = 5760; see table SI, Supplemental Digital Content, http://links.adisonline.com/DSZ/A65). Disproportionality analysis showed a significant ROR for the SOC 'cardiac disorders' (3.04; 95% CI 2.94, 3.14) and 'eye disorders' (1.37; 95% CI 1.27, 1.47), whereas it

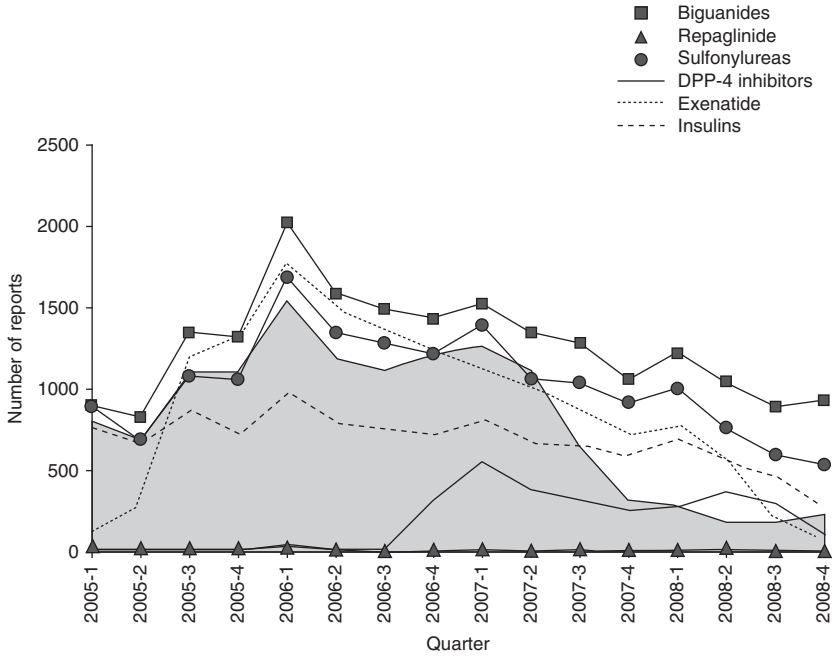

Fig. 1. Trend in spontaneous reporting of ADRs for antidiabetic drugs. **ADRs** = adverse drug reactions. Grey-shaded area = thiazolidediones.

did not find any statistically significant difference for 'injury, poisoning and procedural complications' (1.01; 95% CI 0.96, 1.06), which comprises the SOC for fractures (see table SI, SDC).

Table I shows, for TZDs, the ROR of myocardial infarction, macular oedema and fractures (bone and joint injuries). A significant disproportionality for all the investigated ADRs was found, with RORs of 4.71 (95% CI 4.40, 5.05), 3.88 (95% CI 2.79, 5.39) and 1.73 (95% CI 1.53, 1.96), respectively. Among the other antidiabetic classes, only insulin and gliclazide resulted in a significant ROR for bone and joint injuries (1.23; 95% CI 1.07, 1.42, and 1.51; 95% CI 1.08, 2.09, respectively).

The analysis of the trend of ROR for myocardial infarction showed disproportionality in all quarters observed (figure 2a). In January–March 2005, the ROR value was 3.13 (95% CI 2.38, 4.10). It peaked in October–December 2007 (ROR 8.71; 95% CI 6.02, 12.60), followed by a rapid decrease in the quarters of 2008. The separate analysis of TZDs (table II) showed that only rosiglitazone was associated with myocardial infarction (ROR 7.86; 95% CI 7.34, 8.34).

As to the risk of macular oedema, the low number of cases (67) was insufficient to calculate a trend analysis by quarters because of the large CI range (figure 2b). No changes were observed during the observation period. Also in this case, only rosiglitazone use was associated with this ADR (ROR 5.55; 95% CI 3.94, 7.79; table II).

The disproportionality signal of bone and joint injuries by TZDs first appeared in January–March 2005 (2.70; 95% CI 1.04, 2.78) and became progressively evident in the course of 2007 and 2008 (figure 2c), with a peak ROR to 5.35 (95% CI 2.65, 10.64) in July–September 2008. The ROR was remarkably higher in females than in males (ROR 2.07; 95% CI 1.78, 2.37, and ROR 1.24; 95% CI 0.97, 1.59, respectively). By pooling all the fractures by anatomical site (HLT of MedDRA® terminology), the signal was present for fractures of upper and lower limbs for both drugs, and pelvic fractures only for pioglitazone (data not shown).

Table I. ROR of myocardial infarction, macular oedema and bone and joint injuries for antidiabetic drugs

Therapeutic group	Myocardial infarction[a]			Macular oedema[b]			Bone and joint injuries[c]		
	No. of cases	ROR (95% CI)	pMH	No. of cases	ROR (95% CI)	pMH	No. of cases	ROR (95% CI)	pMH
Biguanides	923	1.05 (0.97, 1.13)	0.201	43	1.10 (0.76, 1.59)	0.583	314	0.86 (0.75, 0.97)	0.153
DPP-4 inhibitors	29	0.33 (0.23, 0.48)	<0.001	0	NA	NA	10	0.29 (0.15, 0.55)	<0.001
Exenatide	58	0.08 (0.06, 0.10)	<0.001	2	0.06 (0.01, 0.25)	<0.001	135	0.51 (0.43, 0.61)	<0.001
Insulins	318	0.56 (0.50, 0.63)	<0.001	9	0.34 (0.16, 0.70)	<0.001	**247**[d]	**1.23 (1.07, 1.42)**	**<0.001**
Repaglinide	1	0.11 (0.01, 0.73)	0.008	1	2.55 (NA)	0.333	5	1.44 (0.53, 3.59)	0.413
Sulfonylureas	484	0.57 (0.51, 0.63)	<0.001	33	0.95 (0.63, 1.41)	0.776	310	1.02 (0.90, 1.17)	0.709
Thiazolidinediones	**1636**	**4.71 (4.40, 5.05)**	**<0.001**	**67**	**3.88 (2.79, 5.39)**	**<0.001**	**347**	**1.73 (1.53, 1.96)**	**<0.001**

a PT: myocardial infarction, acute myocardial infarction, silent myocardial infarction.

b PT: macular oedema, retinal oedema, diabetic retinal oedema.

c HLGT: bone and joint injuries.

d Statistically significant disproportionality (ROR >1 and pMH <0.001) is shown in bold.

DPP-4 = Dipeptidyl peptidase-4; **HLGT** = High-Level Group Term; **NA** = not available; **pMH** = p-value Mantel-Haenszel corrected; **PT** = Preferred Term; **ROR** = reporting odds ratio.

Discussion

Pharmacovigilance is specifically aimed at the early detection of ADRs of marketed drugs. Automated signal detection algorithms are routinely applied to large spontaneous reporting databases.[22,25] Currently, a gold-standard technique is not available and debate exists on the ideal data mining approach – Bayesian[26] or frequentist[27] methods. In this study, ROR was used because of its better performance in terms of sensitivity and timing of early signal detection compared with Bayesian algorithms.[28]

Our analysis showed that the frequency of ADR reporting of myocardial infarction, macular oedema and fractures was significantly higher for TZDs in comparison with other antidiabetic drugs. The signal for myocardial infarction and fractures appeared earlier than major warnings were issued or studies pinpointing the risk were published. The two TZDs showed different risks – rosiglitazone resulted in a significant disproportionality for myocardial infarction and macular edema, whereas pioglitazone showed disproportionaly only for multiple site fractures.

The frequency of reporting was highly variable during the period of the analysis – almost all classes of antidiabetic agents showed a similar trend of ADRs characterized by a very high peak in the first quarter of 2006 and by a continuous decrease throughout 2008. The reasons for these peaks are at present unclear, but a Weber effect can be excluded for TZDs (US marketing launch in 1999) and older antidiabetics (e.g. biguanides). Marketing authorization of new drugs (incretin mimetics and dipeptidyl peptidase-4 inhibitors), as well as the occurrence of severe, unexpected ADRs (pancreatitis), could be the reason for the observed ADR reporting trends. Actually, no parallel trend was found in the entire FDA AERS database, where the number of ADRs is progressively increasing year-by-year.[29] Moreover, the progressive awareness of a possible risk of myocardial infarction with TZDs, together with their frequent coadministration with other antidiabetics, could probably generate a similar reporting trend for all classes. The notable decrease in reporting, especially for TZDs, in the last period of our observation could be partially explained by a substantial decrease in US prescriptions of rosiglitazone in 2007,[30] due to both the concerns on their safety profile and the availability of older and safer therapeutic options.[31] In the field of spontaneous ADR reporting, it is not infrequent that a period of great attention (and reporting) for a given safety concern is followed by a tailing-off of interest; in this case, at the end of 2008 the number of ADRs for most

drugs under scrutiny reverted to those observed in early 2005.

As mentioned above, the most eye-catching result of our analysis is that a signal on TZD-associated myocardial infarction or fractures appeared earlier than the main publications on their safety concern, and even before the relevant safety alerts. Therefore, no notoriety bias should affect disproportionality, but could affect only the overall ROR (2005–8). This finding strengthens the use of the spontaneous ADR reports database as an early source of information on drug safety, in particular for new drugs. The presence of a signal should trigger further studies to substantiate, confirm or refute the pharmacovigilance hypothesis. Clinical trials and meta-analyses remain the best source of evidence, but data mining of large pharmacovigilance databases such as the FDA AERS, as well as observational studies using healthcare registries, may be valuable tools to investigate the safety profile of any given therapeutic class in clinical practice, in the presence of co-morbidities observed in the 'real world' of drug use. In fact, recent studies tried to assess the risks associated with antidiabetics through the analysis of large spontaneous reporting systems.[32,33]

Concerning the warning on TZD-associated fractures, the risk should be taken into account in susceptible patients (e.g. women or men with osteoporosis, long-term corticosteroid recipients, in the elderly). Our data strengthen the already existing precautions of use reported in the pio-

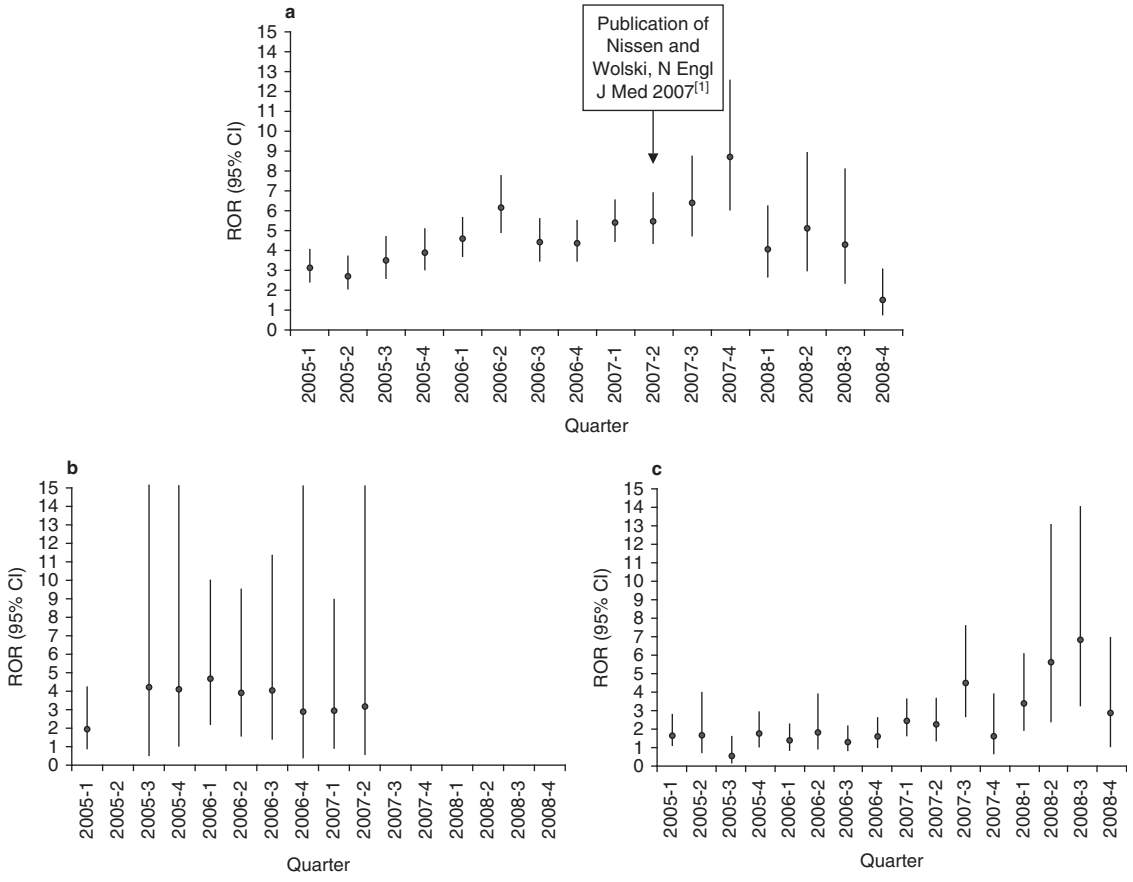

Fig. 2. Quarter-by-quarter ROR trend in (**a**) myocardial infarction; (**b**) macular oedema; and (**c**) bone and joint injuries for thiazolidinediones. **ROR** = reporting odds ratio.

Table II. ROR of myocardial infarction, macular oedema and fractures for rosiglitazone and pioglitazone

ADR of interest	Pioglitazone		Rosiglitazone	
	ROR (95% CI)	pMH	ROR (95% CI)	pMH
Myocardial infarction[a]	0.55 (0.46, 0.65)	<0.001	**7.86 (7.34, 8.34)**[b]	<**0.001**
Macular oedema[c]	0.99 (0.51, 1.88)	0.978	**5.55 (3.94, 7.79)**	<**0.001**
Bone and joint injuries[d]	**2.00 (1.70, 2.35)**	<**0.001**	**1.34 (1.14, 1.59)**	<**0.001**

a PT: myocardial infarction, acute myocardial infarction, silent myocardial infarction.

b Statistically significant disproportionality (ROR >1 and pMH <0.001) is shown in bold

c PT: macular oedema, retinal oedema, diabetic retinal oedema.

d HLGT: bone and joint injuries.

ADR = adverse drug reaction; **HLGT** = High-Level Group Term; **pMH** = p-value Mantel-Haenszel corrected; **PT** = Preferred Term; **ROR** = reporting odds ratio.

glitazone Summary of Product Characteristics in this group of patients[34] and suggest the need for additional observational studies to quantify the relative risk of the old and the new TZDs on the horizon.

Also, the potential risk of macular oedema, which is strongly related to rosiglitazone treatment (relevant increase in ROR from SOC to PT), requires consideration in high-risk patients such as diabetic individuals.

We acknowledge a number of limitations that should be taken into account when interpreting the results obtained from spontaneous report analysis: (a) duplicates, missing data, misspelling of drug names; (b) underreporting; (c) overreporting for drugs involved in safety alerts or regulatory measures (the so-called 'notoriety bias', already discussed above); and (d) dependence of reporting rate by time on the market of each drug (the so-called 'Weber effect').[25,35-39] Concerning myocardial infarction and ocular damage, confounding by indications should also be considered. In particular, these two unwanted effects were also inherent in the progression of the disease and therefore a high rate of these reports should be considered as expected. However, in the calculation of ROR, we compared TZDs with other antidiabetic agents, and the comparison strongly limits this sort of bias. Finally, TZDs represent a second-line treatment in subjects who do not achieve or sustain the glycaemic goals with the maximal tolerated dose of metformin.[40] As such, TZD-treated subjects may be affected by a more advanced or severe stage of diabetes, and may be at increased risk of cardiovascular events and ocular damage. This confounder, the so-called channelling bias, cannot be fully removed by our approach.[41]

Conclusions

Our findings showed that signals for myocardial infarction and fractures from the FDA AERS database were detectable 2 years before the main publications on the relevant safety concerns. Moreover, these results are consistent with observational and experimental studies and in line with the recent regulatory decisions – the FDA hardly restricted use of rosiglitazone to patients who cannot control their diabetes on other medications, whereas the EMA finally decided to withdraw the drug from the market because of the risk of coronary events.[12]

The frequency of ADRs of myocardial infarction, macular oedema and fractures was significantly higher for TZDs in comparison with other glucose-lowering drugs for the treatment of type 2 diabetes, with significant intraclass differences. Rosiglitazone showed a significant disproportionality for myocardial infarction and macular oedema, whereas pioglitazone was only associated with multiple site fractures.

This kind of study might thus represent an important source of evidence to generate early hypothesis on the risk profile of drugs. If performed in a timely manner, it should guide the planning of observational studies. Public access and availability of raw data increase transpar-

ency, and the periodic publication of signals raised by data mining, routinely performed by international regulatory agencies (the FDA, EMA and WHO) could be an additional opportunity to increase collaboration among Regulatory Agencies, pharmacovigilance researchers and manufacturers. This process should guide efforts towards in-depth examination of emerging safety issues and allow timely regulatory measures.

Acknowledgements

This research was supported by institutional funds from the University of Bologna. The authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356: 2457-71
2. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298: 1189-95
3. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med 2010; 170 (14): 1191-201
4. Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007; 298: 1180-8
5. Bilik D, McEwen LN, Brown MB, et al. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). Pharmacoepidemiol Drug Saf 2010; 19: 715-21
6. Bodmer M, Meier C, Kraenzlin ME, et al. Risk of fractures with glitazones: a critical review of the evidence to date. Drug Saf 2009; 32: 539-47
7. Dormuth CR, Carney G, Carleton B, et al. Thiazolidinediones and fractures in men and women. Arch Intern Med 2009; 169: 1395-402
8. Douglas IJ, Evans SJ, Pocock S, et al. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med 2009; 6: e1000154
9. Habib ZA, Havstad SL, Wells K, et al. Thiazolidinedione use and the longitudinal risk of fractures in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2010; 95: 592-600
10. Merante D, Menchini F, Truitt KE, et al. Diabetic macular edema: correlations with available diabetes therapies-evidence across a qualitative review of published literature from MEDLINE and EMBASE. Drug Saf 2010; 33: 643-52
11. Food and Drug Administration. FDA significantly restricts access to the diabetes drug Avandia [online]. Available from URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm [Accessed 2010 Oct 25]
12. European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf [Accessed 2012 Feb 14]
13. Kessler DA. Introducing MEDWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993; 269: 2765-8
14. Brown EG. Using MedDRA: implications for risk management. Drug Saf 2004; 27: 591-602
15. US FDA. The Adverse Event Reporting System (AERS): latest quarterly data files [online]. Available from URL: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm082193 [Accessed 2012 Jan 20]
16. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2010 [online]. Available from URL: http://www.whocc.no/atc_ddd_index/ [Accessed 2010 Aug 30]
17. EUROMEDSTAT. EUROMEDSTAT: a project funded by the European Commission [online]. Available from URL: http://ec.europa.eu/health/ph_projects/2001/monitoring/fp_monitoring_2001_frep_12_1_en.pdf [Accessed 2012 Feb 27]
18. Food and Drug Administration. Drugs@FDA [online]. Available from URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [Accessed 2010 Aug 30]
19. Egberts AC, Meyboom RH, van Puijenbroek EP. Use of measures of disproportionality in pharmacovigilance: three Dutch examples. Drug Saf 2002; 25: 453-8
20. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. Br J Clin Pharmacol 1997; 44: 513-8
21. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009; 18: 427-36
22. Hauben M, Madigan D, Gerrits CM, et al. The role of data mining in pharmacovigilance. Expert Opin Drug Saf 2005; 4: 929-48
23. Almenoff JS, Pattishall EN, Gibbs TG, et al. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther 2007; 82: 157-66
24. Centers for Disease Control and Prevention. Epi Info™ [online]. Available from URL: http://www.cdc.gov/epiinfo/ [Accessed 2010 Aug 30]
25. Almenoff J, Tonning JM, Gould AL, et al. Perspectives on the use of data mining in pharmaco-vigilance. Drug Saf 2005; 28: 981-1007
26. Ahmed I, Thiessard F, Miremont-Salame G, et al. Pharmacovigilance data mining with methods based on false discovery rates: a comparative simulation study. Clin Pharmacol Ther 2010; 88: 492-8
27. van Puijenbroek EP, Bate A, Leufkens HG, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf 2002; 11: 3-10
28. Chen Yan, Guo JJ, Steinbuch M, et al. Comparison of sensitivity and timing of early signal detection of four frequently used signal detection methods: an empirical study based on the US FDA Adverse Event Reporting System Database. Pharm Med 2008; 22: 359-65

29. Food and Drug Administration. Reports received and reports entered into AERS by year [online]. Available from URL: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm [Accessed 2010 Aug 30]
30. Cohen A, Rabbani A, Shah N, et al. Changes in glitazone use among office-based physicians in the U.S., 2003-2009. Diabetes Care 2010; 33: 823-5
31. Shah ND, Montori VM, Krumholz HM, et al. Responding to an FDA warning: geographic variation in the use of rosiglitazone. N Engl J Med 2010; 363: 2081-4
32. Piccinni C, Motola D, Marchesini G, et al. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. Diabetes Care 2011; 34 (6): 1369-71
33. Willemen MJ, Mantel-Teeuwisse AK, Straus SM, et al. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care 2011; 34: 369-74
34. Allegato I: riassunto delle caratteristiche del prodotto [online]. Available from URL: http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/000285/WC500021386.pdf [Accessed 2012 Jan 20]
35. Hauben M, Patadia V, Gerrits C, et al. Data mining in pharmacovigilance: the need for a balanced perspective. Drug Saf 2005; 28: 835-42
36. Hauben M, Reich L, DeMicco J, et al. 'Extreme duplication' in the US FDA Adverse Events Reporting System database. Drug Saf 2007; 30: 551-4
37. Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. Pharmacotherapy 2004; 24: 743-9
38. Pariente A, Gregoire F, Fourrier-Reglat A, et al. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf 2007; 30: 891-8
39. Stephenson WP, Hauben M. Data mining for signals in spontaneous reporting databases: proceed with caution. Pharmacoepidemiol Drug Saf 2007; 16: 359-65
40. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32: 193-203
41. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Stat Med 1991; 10: 577-81

Correspondence: Dr *Domenico Motola*, Department of Pharmacology, University of Bologna, Via Irnerio 48, 40126 Bologna, Italy.
E-mail: domenico.motola@unibo.it