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Influence of Regulatory Measures on the Rate of Spontaneous Adverse Drug Reaction Reporting in Italy

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Abstract

Background: The reporting of adverse drug reactions (ADRs) is the mainstay of post-marketing surveillance systems. Under-reporting and selective reporting are considered the main limitations of a spontaneous reporting-based pharmacovigilance system. However, excessive reporting induced by external events may also impair signal detection by increasing the noise level.

Objective: The aim of this study was to examine the influence of regulatory measures and other external factors on the rate of ADR reporting in Italy, focusing on four situations occurring in the last 10 years: ACE inhibitor-induced cough; HMG-CoA reductase inhibitors ('statins') and rhabdomyolysis; nimesulide and hepatic toxicity; and cyclo-oxygenase (COX)-2 selective inhibitors ('coxibs') and increase in cardiovascular risk.

Methods: The study was based on data from spontaneous reporting in six Italian regions collected from January 1995 to December 2005. We analysed a 10-year period as a reasonable time interval around the four situations of interest, highlighting the influence of regulatory measures on the rate of ADR reporting (number of reports per million inhabitants). Chi-squared tests were used to assess the statistical significance of any changes in ADR reporting. Drug sales data were also studied to examine possible changes in drug use. Sales data were expressed as daily defined dose per 1000 inhabitants per day.

Results: *ACE inhibitors*: a 5-fold increase in the reporting rate of ACE inhibitor-induced cough was observed in 1998 and 1999 following a restriction on reimbursement for angiotensin receptor blockers introduced in 1998 and removed at the end of 1999. *Statins*: after the withdrawal of cerivastatin in 2001, the ADR reporting rate increased more than 4-fold, with musculoskeletal ADRs representing about 60% of all the ADRs reported in that year, and progressively decreased in the following years. *Nimesulide*: an increase in hepatic ADR reporting was observed after withdrawal of the drug from the Finnish and Spanish markets in 2002. *Coxibs*: no important changes in the rate of cardiovascular events reporting in the period 2000–4 were observed. In 2005, after the withdrawal of rofecoxib in September 2004, both the ADR reporting rate and sales of the drug decreased drastically.

Conclusion: Our data suggest that spontaneous ADR reporting can be influenced in different ways by external events. Our data emphasize the need for educational initiatives aimed at increasing the doctor's and patient's awareness of the usefulness and the limitations of spontaneous reporting in the pharmacovigilance system. Such initiatives should use appropriate risk communication strategies in order to avoid unnecessary alarm, which could cause unjustified interruption of therapies or misplaced confidence in new drugs.

Background and Aim

Reporting of suspected adverse drug reactions (ADRs) by doctors and other healthcare professionals is the mainstay of the post-marketing surveillance systems (pharmacovigilance). The main purpose of pharmacovigilance is the early detection of previously unrecognized ADRs and their assessment and understanding, given the usually limited observations possible during pre-marketing clinical trials of new drugs (i.e. strict inclusion criteria, a small number of subjects and the short duration of clinical trials).

Although reporting of a suspected ADR is mandatory in some European countries, the final decision as to whether or not to submit an ADR report may be based on the physician's (or pharmacist's) individual attitude towards spontaneous reporting. Therefore, under-reporting and selective reporting are considered the main limitations of a spontaneous report-based pharmacovigilance system.[1] Furthermore, the 'Weber effect', notoriety bias and other types of induced reporting could increase the noise level, thus impairing signal detection.[2-5]

The aim of this study was to examine the influence of regulatory measures and other external factors on the rate of ADR reporting in Italy, focusing on four different situations occurring in the last 10 years: ACE inhibitor-induced cough; HMG-Co-A reductase inhibitors ('statins') and rhabdomyolysis; nimesulide and hepatic toxicity; and cyclo-oxygenase (COX)-2 selective inhibitors ('coxibs') and increase in cardiovascular risk.

Methods

The study was based on data from spontaneous reporting in six Italian regions, which maintain a pooled ADR database (The Italian Interregional Group of Pharmacovigilance, Gruppo Interregionale di Farmacovigilanza [GIF]): Veneto (since 1988), Lombardia (since 1993), Provincia Autonoma di Trento (since 1994), Sicilia (since 1996), Emilia Romagna (since 2000) and Friuli Venezia Giulia (since 2002).

In 2005, the GIF regions had a population of about 23.7 million inhabitants (42% of the Italian general population), and collected more than 60% of all Italian ADRs.[6,7] In each regional centre, the reports were reviewed by medically qualified personnel (physicians or pharmacists) before being loaded onto the database.[8,9]

All ADR reports from January 1995 to December 2005 concerning the following drugs were retrieved from the GIF database: ACE inhibitors (Anatomical Therapeutic Chemical [ATC] classification codes C09A, C09B); statins (ATC code C10AA); nimesulide (ATC code M01AX17); and coxibs (ATC code M01AH). A 10-year period was considered a reliable time interval to highlight the influence of external factors on the rate of ADR reporting for the events of interest.

As the regions joined the GIF database progressively, the data were expressed as the number of ADR reports per million inhabitants (reporting rate), using the population of the regions present in the database in the considered year as the reference population.

Chi-squared tests were performed by comparing the reporting rate for the considered ADR in the year of the event with that of the previous year. Similar comparisons for the following years versus the year before the event were also performed in order to assess the persistence of the observed effect.

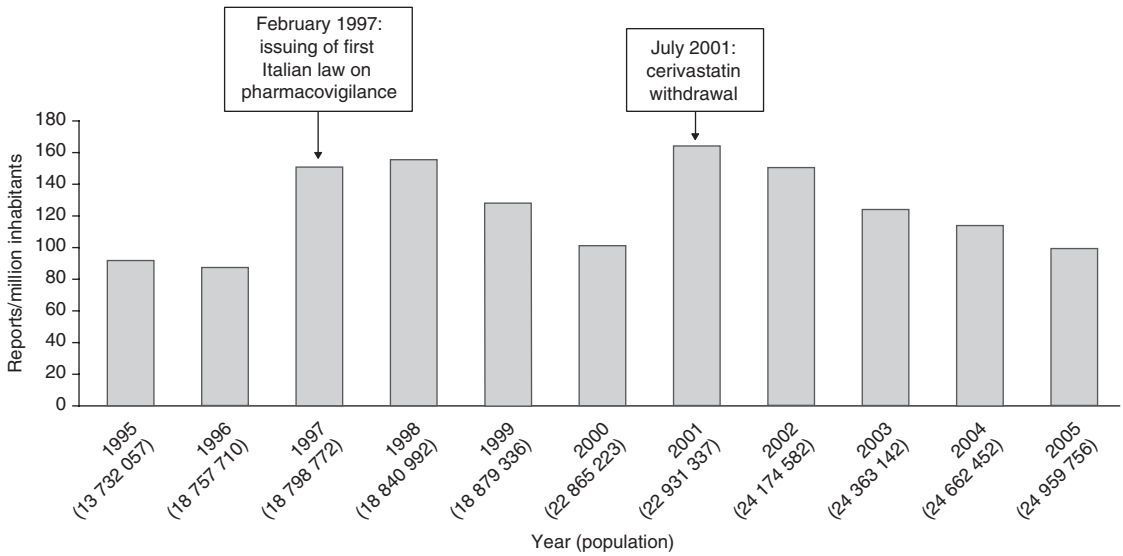

Fig. 1. Adverse drug reaction reporting rate in the Italian Interregional Group of Pharmacovigilance (Gruppo Interregionale di Farmacovigilanza) region in the period 1995–2005.

The national sales data from Intercontinental Medical Statistics (IMS) Health for the drugs under scrutiny were supplied by the National Drug Utilisation Monitoring Centre (OsMed).[10] Drug consumption was expressed as defined daily doses (DDD) per 1000 inhabitants per day.

Results

Figure 1 shows the time trend for the rate of ADR reports per million inhabitants in the GIF regions. In 1997, an important increase in the number of ADR reports was observed (+75% compared with 1996), coinciding with the issuing of the first Italian law concerning pharmacovigilance, which obliged doctors to report all the ADRs they detected. Another important peak (+65% compared with the previous year) was observed in 2001 after the withdrawal of cerivastatin, with a slight decrease in the following years.

Case 1: ACE Inhibitors and Cough

ACE inhibitors are commonly used for the treatment of hypertension and heart failure. They are generally well tolerated, apart from uncommon episodes of angioneurotic oedema, and their most important although non-serious ADR is cough. By 1995, all the different ACE inhibitors (13 compounds) were on the market in Italy apart from zofenopril, first marketed in 1999. Until 1997, there were fewer than 100 ADR reports per year for ACE inhibitors in the GIF area, with a reporting rate of less than six reports per million inhabitants (figure 2). Cough represented about 50% of all reports. Angiotensin receptor blockers (ARBs), characterized by a lower occurrence of dry cough, were introduced in 1995 and admitted to reimbursement in 1997, with a relevant impact on drug expenditure. In 1998, the Italian Ministry of Health, owing to the higher price of ARBs and to a lack of evidence on their long-term benefits at that time, restricted reimbursement to patients who had to discontinue treatment with an ACE inhibitor because of intolerable cough. This regulatory measure led to about a 5-fold increase in the reporting rate of cough in 1998 and 1999, whereas the number of all other ADRs remained unchanged (figure 2). Chi-squared for cough over the entire period of 1995–2005 was highly significant (178.76; degrees of freedom [d.f.] = 10; $p < 0.001$). The results of the single 2×2 chi-squared tests concerning 1998 versus 1997 and 1999 versus 1997 were statistically significant (31.44;

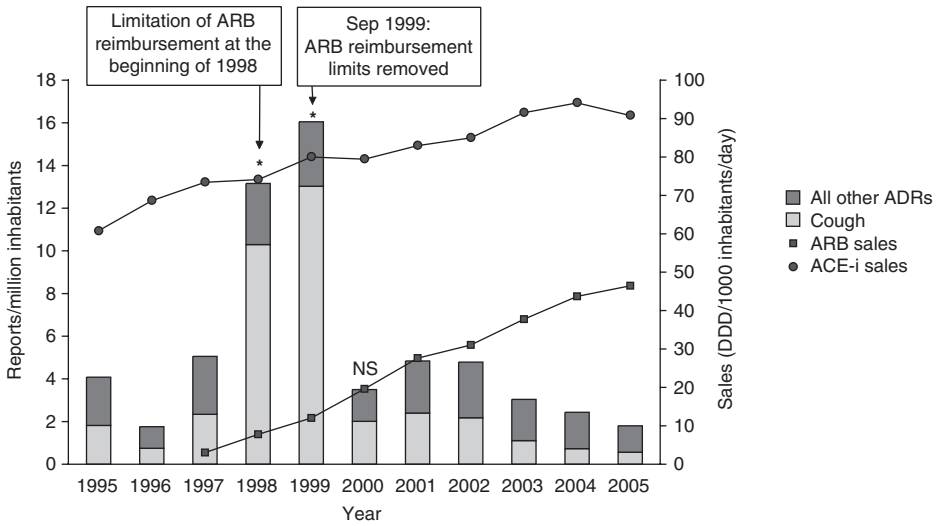

Fig. 2. Adverse drug reaction (ADR) reporting rate and daily defined dose (DDD)/1000 inhabitants/day for ACE inhibitors (ACE-i) and angiotensin receptor blockers (ARBs). **NS** = not significant vs 1997; * $p < 0.001$ vs 1997.

$p < 0.001$ and 42.74; $p < 0.001$, respectively). The reimbursement restriction of ARBs was removed at the end of 1999, and the ADR reporting rate in 2000 returned to the level of 1997. The proportion of cough reports decreased concomitantly in the following years.

Most reports of ACE inhibitor-induced cough in 1998–9 concerned the oldest drugs such as enalapril, lisinopril, fosinopril, ramipril and captopril, in accordance with their extent of use.

Figure 2 also shows the trends of ACE inhibitors and ARB sales in the period 1995–2005. The sales of ACE inhibitors increased progressively from 60.8 DDD/1000 inhabitants/day in 1995 to 90.8 DDD/1000 inhabitants/day in 2005, whereas the sales of ARBs showed a much greater increase in the period 1997–2005, from 3.0 DDD/1000 inhabitants/day to 46.4 DDD/1000 inhabitants/day.

Case 2: Statins and Rhabdomyolysis

At the end of July 2001, news of the 'Lipobay' case broke out and received extensive media coverage. Among the users of the newly marketed statin cerivastatin, about 100 cases of fatal rhabdomyolysis and acute renal failure occurred worldwide when the drug was used either as monotherapy or concomitantly with other drugs acting as metabolizing enzyme inhibitors. The drug was withdrawn immediately in Europe[11] and the US.[12] In 2001, five statins were available on the Italian market (atorvastatin, cerivastatin, fluvastatin, pravastatin and simvastatin). As figure 3 shows, the reporting rate of all ADRs for statins before 2001 was less than five reports per million inhabitants with a proportion of musculoskeletal ADRs of about 20–40%. In 2001, the reporting rate increased more than 4-fold (to 24 reports per million inhabitants), musculoskeletal ADRs representing about 60% of all the ADRs reported in that year (326 of 545). In terms of number of reports, ADRs for cerivastatin represented 40% of all reports in 2001 (219 of 545), followed by 25% for simvastatin (135 of 545), 22% for atorvastatin (120 of 545), 10% for pravastatin (52 of 545) and 3% for fluvastatin (19 of 545). Chi-squared for musculoskeletal ADR over the entire period of 1995–2005 was highly significant (97.56; d.f. = 10; $p < 0.001$). The 2×2 chi-squared for the year 2001 versus 2000 was 5.31 ($p < 0.05$), whereas comparisons for the following years were not significant.

The reporting rate showed a decrease after 2001 and in 2005 returned to a level similar to that seen before 2001. As for statin sales, a continuous increase from 4.7 DDD/1000 inhabitants/day in 1995

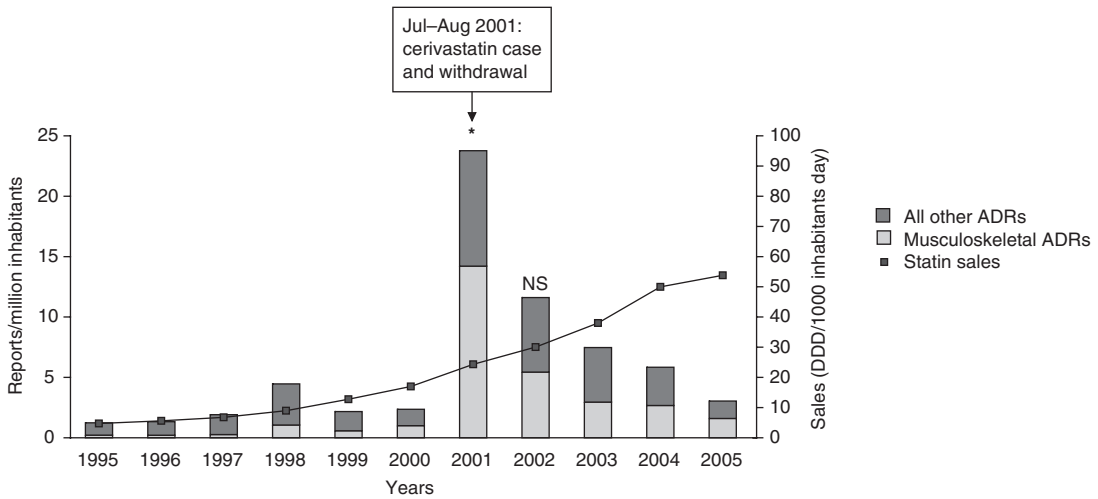

Fig. 3. Adverse drug reaction (ADR) reporting rate and daily defined dose (DDD)/1000 inhabitants/day for statins. **NS** = not significant vs 2000; * $p < 0.05$ vs 2000.

to 53.8 DDD/1000 inhabitants/day in 2005 was observed (figure 3).

Case 3: Nimesulide and Hepatic Toxicity

Nimesulide was first marketed in Italy in 1985 and, since then, it has been the most widely used NSAID in Italy. It was withdrawn from the Finnish and Spanish markets during 2002 in response to spontaneous reports of serious hepatic ADRs, some of which were fatal. The regulatory agencies of other European countries such as Italy and France did not impose any restrictions on prescribing at that time.

After the news of the withdrawal of nimesulide (which appeared only in medical journals and regulatory bulletins), we observed a small increase in the reporting rate of all ADRs in the GIF region (figure 4), but an important increase in the proportion of hepatic ADRs, which rose from about 5% before 2002 to about 20% in the period 2002–5. Chi-squared for hepatic ADR over the entire period of 1995–2005 was highly significant (60.16; d.f. = 10; $p < 0.001$). The 2×2 chi-squared for 2002 versus 2001 was statistically significant (9.57; $p < 0.002$), and this significance persisted in the following years. On the other hand, the period 1995–2001 did not show significant differences (chi-squared =

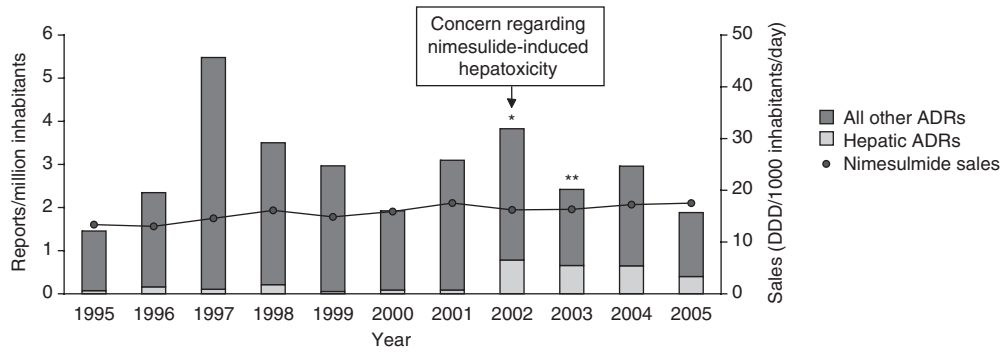

Fig. 4. Adverse drug reaction (ADR) reporting rate and daily defined dose (DDD)/1000 inhabitants/day for nimesulide. * $p < 0.002$ vs 2001; ** $p < 0.001$ vs 2001.

4.01; d.f. = 6; p = 0.673). In the same years, sales of nimesulide remained stable.

Case 4: Coxibs and Cardiovascular Toxicity

Rofecoxib is an NSAID belonging to the new class of coxibs, first marketed in the US in 1999 and then in Italy in 2000, with the claim of a more favourable benefit/risk profile in terms of gastrointestinal risk in comparison with the traditional naproxen in the treatment of osteoarthritis-associated pain.[13] In September 2004, the manufacturer withdrew the drug voluntarily from the worldwide market owing to an increase in serious cardiovascular toxicity (myocardial infarction and stroke) seen during the APPROVe (Adenomatous Polyp Prevention On Vioxx[1]) trial.[14] For the same reasons, in addition to concern about serious skin reactions, valdecoxib was withdrawn from the US market in 2005.[15,16] Unlike the safety concerns regarding cerivastatin, this new safety concern was not particularly emphasized by the media in Italy, with coverage being restricted to medical and regulatory bulletins and clinical literature. The reports of ADRs with coxibs in the GIF region amounted to 100–200 reports in 2000, 2002 and 2003 (reporting rate four to six per million inhabitants, figure 5), but exceeded 200 reports in 2001 (possibly as a result of the 'driving effect' of cerivastatin and/or the so-called 'Weber effect', since rofecoxib and celecoxib were first marketed in 2000). We did not observe important changes in the proportion of cardiovascular reports in the period 2000–4. Chi-squared for cardiovascular ADR over the entire period of 2000–5 was not significant (7.85; d.f. = 5; p = 0.18); neither was the 2×2 test for 2004 chi-squared versus 2003.

In 2005, a drastic decrease in the reporting rate was observed, coinciding with a decline in sales (figure 5). Overall, coxib consumption increased from 2.7 DDD/1000 inhabitants/day in 2000 to 11.1 DDD/1000 inhabitants/day in 2004, and dropped dramatically to 4.3 DDD/1000 inhabitants/day in 2005. This was not only attributable to rofecoxib withdrawal; a similar trend was observed when rofecoxib sales data were excluded.

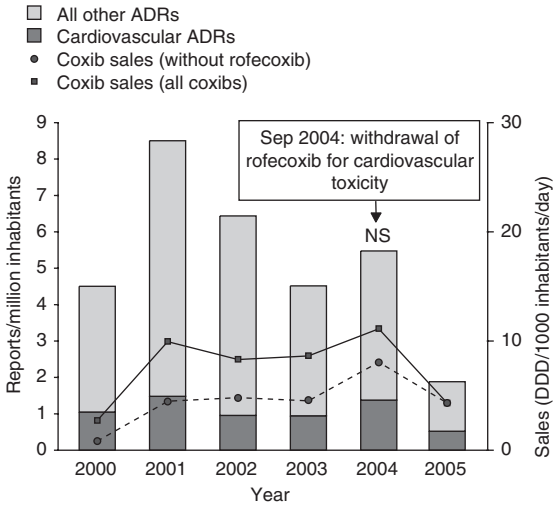

Fig. 5. Adverse drug reaction (ADR) reporting rate and daily defined dose (DDD)/1000 inhabitants/day for coxibs. **NS** = not significant vs 2003.

Discussion

Our data suggest that spontaneous ADR reporting can be influenced in different ways by external events. The examples chosen are representative of four different types of possible external influences on spontaneous reporting: ACE inhibitor-induced cough as an example of a reimbursement restriction; statin-induced rhabdomyolysis as an example of safety concerns amplified by the mass media; nimesulide-induced hepatic toxicity as an example of safety concerns originating in another country and coxib-induced increased cardiovascular risk as an example of a safety concern resulting from the spontaneous withdrawal of a drug.

In the case of ACE inhibitors, general practitioners (GPs) frequently reported cough as a motivation to switch their patients to ARBs, which could also be presented as the reason for the switch in the event of prescription audit by the local health authority. When the restriction on reimbursement for ARBs was removed, the number of ACE inhibitor ADR

1 The use of trade names is for product identification purposes only and does not imply endorsement.

reports returned to the levels of 1997. Similar findings were reported by Cosentino et al.,[1] who found a clear correlation between ARB reimbursement status and the reporting of ACE inhibitor-associated cough.

The case of cerivastatin in 2001 shook the pharmacovigilance system and promoted a general increase in ADR reporting, which persisted in the following years. Moreover, the case of cerivastatin highlights (i) the unsuitability of the premarketing clinical studies in the detection of rare, serious and even lethal ADRs; (ii) the failure of post-marketing pharmacovigilance systems in safeguarding patients from these events;[17] and (iii) the inclination of GPs to prescribe new drugs even when the parent drugs have a well established place in therapy and a better known safety profile.

In the case of nimesulide, Italian users and doctors were 'reassured' by a pharmacoepidemiological study documenting a small risk of liver toxicity,[18] and by a 'Dear Doctor' letter in 2002 from the Italian Ministry of Health[19] advising about the appropriate use of the drug. Indeed, most prescriptions for nimesulide in Italy were related to the short-term treatment of painful and inflammatory conditions (e.g. toothache, headache, unspecified pain, etc.), whereas the pattern of use in Finland (where the drug was withdrawn in 2002) was different (long-term treatment, high dosage). However, in May 2007, the Irish Medicines Board (IMB) announced the immediate suspension of marketing and sale of oral nimesulide-containing products available in Ireland following reports of a number of cases of fulminant hepatic failure requiring liver transplantation associated with use of nimesulide.[20] The IMB requested a new referral to the Committee for Medicinal Products for Human Use (CHMP) at the European Agency for the Evaluation of Medicinal Products (EMEA). On 21 September 2007, the Committee concluded that the benefits of nimesulide outweigh its risks, but there is a need to restrict its use and limit the duration of therapy to ensure that the risk of patients developing liver problems is kept to a minimum.[21]

The rofecoxib case has been judged as one of the greatest drug safety catastrophes.[22] In Italy, the sales of the remaining COX-2 inhibitors declined markedly, probably because of safety concerns but also as a result of the increasing awareness that COX-2 inhibitors are similar to older NSAIDs in terms of efficacy and only slightly better in terms of gastrointestinal safety.[23-25]

Conclusion

A spontaneous reporting system is a cornerstone for signal detection analyses but situations such as those described in the present report may hamper this process. Since all the automated signal detection procedures and data mining techniques are based on an unexpected disproportionate reporting of an event associated with a drug in comparison with the same event for all the other drugs in the database, our examples show that external influences could act as confounding factors, selectively increasing the proportion of some reactions in the database.

Moreover, drug manufacturers should also contribute to efforts to ensure the safety of patients by earlier disclosure of protected data on new suspected ADRs before the widespread use of drugs in the population. This would have prevented several serious and often lethal cases of rhabdomyolysis with cerivastatin[26] and cardiovascular events with rofecoxib.[27,28]

In conclusion, our data emphasize the need for educational initiatives aimed at increasing the doctor's and patient's awareness of the usefulness and the limitations of the spontaneous reports pharmacovigilance system. Such initiatives should use appropriate risk communication strategies in order to avoid unnecessary alarm, which could cause unjustified interruption of therapies or misplaced confidence in new drugs.

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