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CURRENT OPINION

Scientific Evidence and Controversies About Pioglitazone and Bladder Cancer: Which Lessons Can Be Drawn?

Jean-Luc Faillie · Pierre Petit · Jean-Louis Montastruc · Dominique Hillaire-Buys

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Abstract Pioglitazone, a peroxisome proliferator-activated receptors (PPAR) agonist, has been authorized for the management of type 2 diabetes since 1999 in the US and since 2000 in Europe. Since then, the risk of bladder cancer associated with pioglitazone use has been a serious concern. Following a warning from the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) [the French Agency for the Safety of Health Products], use of pioglitazone was suspended in France and Germany in June 2011. Elsewhere, restrictions on prescriptions were implemented, though for both the European Medicines Agency and the US Food and Drug Administration, the risk-benefit ratio remains favourable. Since the development of pioglitazone, its risk assessment has suffered from several inaccuracies such as its alleged specificity for the male rat, untrustworthy selective agonism for PPARγ and mistaken risk evaluation in the large PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events), where one case with a benign tumour in the placebo group was counted as a cancer case. It took until 2011 for the epidemiological data to be sufficiently numerous and conclusive to initiate application of safety measures. Today, the increased risk of bladder cancer associated with pioglitazone seems to be real, but the absolute risk is relatively low. However, in the context of weak efficacy in an extensive population of patients exposed to pioglitazone, the risk-benefit balance is now difficult to assess, and prescription restrictions do not ensure safety. For future risk management, the authors propose several suggestions, which involve an increasing role of health authorities and academic organizations.

J.-L. Faillie (✉) · P. Petit
Département de Pharmacologie Médicale et Toxicologie, Centre Régional de PharmacoVigilance, CHRU Montpellier, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier, France
e-mail: jl-faillie@chu-montpellier.fr

J.-L. Faillie
Equipe de PharmacoEpidémiologie INSERM U1027, Faculté de Médecine, Université Paul-Sabatier, Toulouse, France

J.-L. Montastruc
Service de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de PharmacoVigilance, de PharmacoEpidémiologie et d'Informations sur le Médicament, Equipe de PharmacoEpidémiologie INSERM U1027, Faculté de Médecine et CHU, Université Paul-Sabatier, Toulouse, France

D. Hillaire-Buys
Département de Pharmacologie Médicale et Toxicologie, Centre Régional de PharmacoVigilance, INSERM U1058, Faculté de Médecine et CHRU, Montpellier, France

1 Background

Since the 1990s, peroxisome proliferator-activated receptors (PPARs) have been thought to play an important role in metabolic diseases such as obesity, insulin resistance and coronary artery disease. Three subtypes of PPAR nuclear receptors have been described: PPARα, PPARδ/β and PPARγ. PPARα is found in the liver, muscle, kidney and heart. Its role is to increase free fatty-acid oxidation, to regulate lipoprotein concentrations and to provide anti-inflammatory effects. Fibrates belong to the class of PPARα agonists. PPARδ/β is expressed in many tissues but markedly in the brain, adipose tissue and skin. PPARγ has high expression in fat and low expression in the liver and muscle tissue. Thiazolidinediones (TZD), also called 'glitazones', are said to be synthetic ligands of PPARγ. By activating a number of genes in tissues, PPARγ agonists increase glucose and lipid uptake, increase glucose

oxidation, decrease free fatty-acid concentrations and decrease insulin resistance [1]. Three glitazones have been marketed for the management of type 2 diabetes mellitus: troglitazone, rosiglitazone and pioglitazone. The first to be marketed, troglitazone, was withdrawn in 2000 for hepatotoxicity [2]. Rosiglitazone, authorized in 2000, was also withdrawn from the European market in 2010 following evidence of an association with an increased cardiovascular risk in diabetic patients [3]. Pioglitazone has been authorized for type 2 diabetes since 1999 in the US [4] and since 2000 in Europe [5]. In 2011, worldwide exposure to pioglitazone was estimated at more than 20 million patient-years [6].

In developed countries, bladder cancer is the eighth most frequent cancer (4.1 % of all cancers), with an age-standardized incidence of 9.1 per 100,000 persons per year [7]. Risk factors for bladder cancer include white ethnicity, male gender, age, a personal or family history of bladder cancer, cigarette smoking, bladder birth defects, occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons, drugs (e.g. cyclophosphamide), urinary schistosomiasis or pelvic radiation therapy (effects of low fluid consumption, common urinary tract infections or lithiasis have also been suggested as risk factors but are still controversial).

In 2011, regulatory decisions were taken with respect to the potential risk of bladder cancer associated with pioglitazone use. Following a warning from the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) [the French Agency for the Safety of Health Products], use of pioglitazone was suspended in France and Germany in June 2011 [8, 9]. The product information and prescribing conditions have been updated in the US and in Europe in order to take into account this potential association, though for both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), the risk-benefit ratio remains favourable. Recently published data have made it possible to draw reliable conclusions regarding the existence of the bladder cancer risk associated with pioglitazone use. In order to draw lessons from this controversy, this article reviews the available scientific evidence, from preclinical studies to post-marketing pharmacoepidemiological studies, and discusses the regulatory management of this risk.

2 Biologic Plausibility

2.1 Bladder Cancer in Rats and the Crystalluria Hypothesis

The initial label information for pioglitazone stated that preclinical studies had reported the occurrence of bladder cancer in male rats treated with pioglitazone at a dose equivalent to the recommended human oral dose [10]. In 2005, a review of a 2-year rodent carcinogenicity study of 11 PPAR agonists, including pioglitazone, determined that these compounds were multi-species, multi-sex and multi-site carcinogens [11, 12]. The tumour types that were observed included transitional cell carcinomas of the urothelium in rats of all strains. Regarding pioglitazone, the rationale involved the acidic urinary environment of rats, which predisposed them to formation of urinary microcrystals, causing chronic irritation of the bladder. This so-called 'crystalluria hypothesis' explained the occurrence of tumours secondary to mucosal irritation caused by urinary microcrystals in the ventral part of the bladder. Such a phenomenon was considered specific to rats and unlikely to be transferable to humans [13–16]. To our knowledge, the presence of urothelial calculi in patients participating in subsequent clinical trials was not extensively explored and/or not reported.

Later, conflicting evidence emerged. In 2008, Long et al. [17] concluded that urolithiasis was not an inciting event for urothelial carcinogenesis in the urinary bladders of rats treated with naveglitazar, an in vitro γ-dominant PPARα/γ agonist. In 2011, Sato et al. showed that, while an acid-forming diet reduced both the amount of calculi and the numbers of bladder cancers in male rats, the diet did not reduce the incidence of hyperplasia in animals treated with pioglitazone for up to 2 years [6, 18]. Contradicting the 'crystalluria hypothesis', the hyperplastic response in the urinary bladder of the rat was not necessarily associated with microcrystal formation. These data suggested that occurrence of bladder cancer may not be specific to the urinary environment in rats and, thus, that a risk for humans could not be brushed aside.

2.2 In Vitro Antitumor Effects?

Numerous in vitro studies have supported the hypothesis of antitumor activities of PPARγ agonists, such as growth inhibition, induction of apoptosis and a modulatory effect on the proliferation/differentiation balance in urothelial cells [15, 19–23]. These positive results were inconsistent with observations made in animals (and further in humans) and may consequently illustrate a complex mechanism, which is difficult to elucidate [16]. For instance, it was shown that the potential antiproliferative effect of pioglitazone was smaller than that of an endogenous ligand of PPARγ (15d-PGJ2) or troglitazone (a specific PPARγ agonist) [20]. Furthermore, the positive expression of a differentiation factor for urothelial carcinoma (A-FABP) inversely correlated with pioglitazone concentrations, while those of rosiglitazone and 15d-PGJ2 remained stable [24]. In these in vitro studies, the suspected

antiproliferative (pro-apoptotic) effect was, rather, described as only being effective at a low grade of differentiation, at high concentration [20, 25, 26] and through a mechanism independent of PPARγ agonism [19, 27].

2.3 Promoter and/or Inductor Effect?

Occurrence of bladder cancer in animals with no a priori preclinical lesions nor exposure to additional specific risk factors suggests a mechanism of tumoral induction by the studied drug. This is a strong argument for a causative role of pioglitazone. Another argument for the inductor effect is that pioglitazone may induce chromosomal and oxidative DNA damage by generating reactive oxygen species, which can be inhibited by vitamin B_{12} [28]. However, a promoter effect can also be evoked for PPAR agonists when interaction with other known risk factors leads to potentiation of tumorigenic effects. Several studies have suggested that diabetes can be considered an independent risk factor for bladder cancer [29–31]. Thus, occurrence of bladder cancer within a relatively short period of exposure to pioglitazone in diabetic patients (see the sections on clinical trials and epidemiological studies) could be explained by potentiation with the diabetic condition itself. Other risk factors could also be involved; Lubet et al. [32] showed that the incidence of bladder cancer in rats exposed to hydroxybutyl(butyl)nitrosamine (a urinary bladder-specific carcinogen) was significantly doubled when rosiglitazone was added at a dose equivalent to a standard human dose. Another study demonstrated that mice exposed to cigarette smoke for 6 months associated with a high dose of pioglitazone showed enhanced urothelial tumorogenicity as compared with mice that were only exposed to cigarette smoke [33]. Potentiation was also observed with pioglitazone in a murine model of non-small cell lung cancer in mice: cancer progression and metastasis were promoted [34]. These examples are in favour of a promoter effect, PPARγ agonists accelerating a tumorigenic process that has already been initiated but is still asymptomatic. Thus, in clinical trials and epidemiological studies, it is important to detect and consider all of the bladder cancer cases that have occurred, even with short durations of exposure.

Moreover, another main pharmacological mechanism remains unexplored: the potential role of pioglitazone metabolites. Active metabolites (such as M-III and M-IV) show equal or greater pharmacological action than pioglitazone (up to threefold) with a longer plasma elimination half-life (three- to fourfold) [35]. Pioglitazone is principally metabolized by cytochrome P450 2C8, and by other isoforms to a lesser degree. Enzymatic inductors, such as rifampicin, increase the level of these metabolites and may cause their accumulation in urine [35, 36]. We can also question the role of tobacco, which is a well-known enzymatic inductor. Unfortunately, during development, the search for potentially deleterious effects of pioglitazone metabolites was poorly investigated.

2.4 Pioglitazone: a Glitazar More Than a Glitazone

Pioglitazone has always been described as a selective PPARγ agonist. In order to improve both glucose and lipid metabolic parameters, dual PPARα/γ agonists were developed; these compounds were named 'glitazars'. However, glitazars, such as muraglitazar, have been shown to dose-dependently increase the incidence of bladder tumours in male rats [14]. Between 2004 and 2006, use of all dual PPARα/γ agonists was discontinued because of safety concerns, including the occurrence of bladder tumours in rodents [37]. After careful consideration of pharmacodynamic data published after marketing, pioglitazone cannot be considered a selective PPARγ agonist but in fact exhibits a pharmacological profile comparable to that of glitazars: a dual PPARα/γ activity at concentrations corresponding to human use [38]. Therefore, it may not be surprising that pioglitazone and some glitazars share the same urothelial toxicity.

3 Clinical Trials

3.1 Uncertain Effectiveness of Pioglitazone

During development, reductions in haemoglobin A_{1c} (HbA_{1c}) levels were demonstrated in patients exposed to pioglitazone, but its long-term cardiovascular effectiveness was unknown. The PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROactive) was conducted to assess the cardiovascular benefit of pioglitazone compared with placebo in 5,238 diabetic patients with extensive macrovascular disease [39]. Results published in 2005 indicated that, during a mean follow-up of 34.5 months, a significant 0.5 % decrease in HbA_{1c} was shown in favour of pioglitazone. However, the authors did not observe a statistically significant reduction in the primary composite endpoint, which included all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in coronary or leg arteries, and amputation above the ankle (hazard ratio [HR] 0.90, 95 % confidence interval [CI] 0.80–1.02, $p = 0.095$). They reported a significant reduction in the secondary composite endpoint of death, myocardial infarction or stroke (HR 0.84, 95 % CI 0.72–0.98, $p = 0.027$), a result on which they based their conclusions. It is worth noting that this secondary endpoint was not clearly predefined in the publication of the trial protocol [40]. To defend themselves from post hoc analysis, authors

explained later that this endpoint had been devised during the trial but before data analysis [41]. Despite this statement by the authors, several points limit the evidence resulting from this trial: (i) the trial conclusions were drawn from the results of secondary outcomes; (ii) the trial was placebo controlled and not tested against a reference drug; (iii) the trial included patients with prior evidence of a high cardiovascular risk (this is not a priori representative of pioglitazone-treated patients in real life); and (iv) a significantly increased risk of heart failure was observed in the pioglitazone group [39]. Later, a meta-analysis of randomized controlled trials focusing on cardiovascular events associated with pioglitazone was conducted: 99 trials were selected [42]. Among them, 10 were >12 months in duration and two were >24 months in duration. In total, 16,390 patients were included. Twenty eligible trials (totalling 3,014 patients) not sponsored by the manufacturer were not included in the analysis. A composite endpoint including death, myocardial infarction or stroke was significantly decreased by 18 % in the group of patients receiving pioglitazone. The incidence of serious heart failure was significantly higher in the pioglitazone group (+41 %), and a broader definition of cardiovascular risk combining death, myocardial infarction, stroke and serious heart failure did not show any cardiovascular benefit for pioglitazone (HR 0.96, 95 % CI 0.85–1.09, $p = 0.54$). In 2008, another meta-analysis included 24 randomized trials (excluding PROactive), enrolling 11,268 patients in the pioglitazone group and 9,912 patients in the comparator group. Unfortunately, only summary data without time-to-event information were taken into account, and many of the studies did not have specific cardiovascular endpoints. All-cause mortality was lower in the pioglitazone group (odds ratio [OR] 0.30, 95 % CI 0.14–0.63) but not non-fatal coronary events. The increase in non-fatal heart failure was not statistically significant (OR 1.38, 95 % CI 0.90–2.12). The authors concluded that pioglitazone does not appear to be harmful in terms of cardiovascular events and all-cause mortality [43]. All of these data, taken as a whole, suggest that the clinical efficacy of pioglitazone in reducing cardiovascular events has not been clearly demonstrated, since the methodologies that were used can be criticized.

3.2 Assessment of Bladder Cancer Risk in Clinical Trials

Premarketing clinical trials were often too short, with insufficient sample sizes, and were not specifically designed to measure the occurrence of bladder cancer. In the first report of the PROactive trial, 14/2,605 cases (0.5 %) of bladder neoplasms were reported in the pioglitazone group versus 6/2,633 (0.2 %) in the placebo group; this difference did not reach statistical significance ($p = 0.069$) [39]. An overview of the PROactive data published in 2009 revealed that one case in the placebo group actually exhibited benign histology. Unfortunately, no new estimation of risk was reported at that time [44]. Taking into account only five cancers in the placebo group, the overall incidence was statistically lesser than that in the pioglitazone group: 0.19 % ($n = 5$) versus 0.54 % ($n = 14$), respectively ($p = 0.040$) [45]. The recalculated crude risk ratio (RR) for bladder cancer was 2.83 (95 % CI 1.02–7.85). The authors of the PROactive study explained that after a blinded review of bladder cancer cases, which eliminated the cases who were reported within 1 year of randomization or who showed known risk factors for bladder cancer, only two cases in the pioglitazone group and one in the placebo group were left. The Data and Safety Monitoring Committee concluded that these numbers were too small to consider bladder cancer a safety issue [44]. An extended study was planned to monitor PROactive patients over a longer period (up to 10 years). The results have not been published to date, but interim reports were submitted to the EMA by the manufacturer: a pooled analysis of data from the double-blinded period and the 6-year observational period showed that, overall, bladder cancer was reported in 25 subjects (0.9 %) who received pioglitazone and 20 subjects (0.8 %) who were never exposed to pioglitazone (HR 0.98, 95 % CI 0.6–1.8) [6]. In two other 72-week, double-blinded, randomized, multicenter trials conducted between 2003 and 2006, the incidence of bladder neoplasms was not reported [46, 47].

4 Observational Studies

4.1 Analysis of Spontaneous Reports

In a review of cases based on spontaneous reports within the manufacturer's global database, 68 cases of bladder cancer associated with pioglitazone were found for the period 31 July 1999 to 15 March 2011 [6]. After elimination of cases with confounding factors, there were 13 cases left. Fourteen additional cases (including one patient who died as a result of cerebral metastasis) were found in the EudraVigilance database from 16 March 2011 to 24 May 2011, which leads to 82 cases in total.

In June 2011, in an independent case/non-case analysis from the FDA Adverse Event Reporting System (AERS) database, Piccinni et al. [48] found 31 cases associated with pioglitazone between the years 2004 and 2009; the reporting odds ratio (ROR) was 4.30 (95 % CI 2.82–6.52). ROR measures the disproportionality of reporting in pharmacovigilance databases; although it cannot fully be interpreted as a RR, these findings supported a significant

risk of bladder cancer associated with pioglitazone. However, analysis of adverse event reporting databases is always susceptible to reporting bias due to important under-reporting. Conversely, over-reporting can be observed as a result of media or notoriety bias. In order to take this phenomenon into account, the authors performed a year-by-year analysis and found a significant relationship as early as 2004 (ROR 4.77, 95 % CI 1.30–15.88), i.e. before the first PROactive publication [48].

4.2 Studies Using Large Medical Databases

Table 1 presents the design and characteristics of the principal observational studies focusing on the bladder cancer risk associated with pioglitazone use. The results and comments are shown in Table 2.

4.3 Inherent Limits of Observational Studies

Observational studies that evaluate the risk of bladder cancer associated with pioglitazone use are susceptible to numerous biases, which can potentially limit the interpretation of their results. Firstly (as can also be criticized with regard to randomized controlled trials), the duration of follow-up in the available observational studies could be often too short to detect the occurrence of cancer—specifically, induced cancer. For the study of promoted cancer, shorter durations of follow-up may be sufficient. Secondly, even if some studies use very large medical databases, analysis of rare events (which is the case here) sometimes cannot involve enough cases to provide sufficient statistical power. Thirdly, it seems that patients with type 2 diabetes show an increased risk of bladder cancer [29–31] and that this risk increases with the duration of diabetes [30]. Consequently, observational studies have to deal with the risk of errors related to the potential difference in the severity of diabetes between patients exposed to pioglitazone and other diabetic patients. As pioglitazone is often prescribed as a second-line therapy, indication bias represents a major issue, which can partially be taken into account in adjustment of the results for the duration of diabetes or the duration of therapy. For the same reason, it is important that these studies include elderly patients. Fourthly, changes in pharmacotherapy over time can be frequent in patients with type 2 diabetes; these changes cannot always be considered or may require complex analyses that limit interpretation. In addition, information bias is often difficult to rule out: in numerous observational studies, prescription of glucose-lowering agents has been used as a proxy for the definition of diabetes. Drug use is also defined by prescriptions written by practitioners or dispensed in pharmacies. Thus, it is difficult to know whether these prescriptions correspond to actual exposure. Bladder cancer occurrence mentioned in health insurance databases, hospital discharge diagnosis records or primary care medical records are also subject to potentially substantial information bias, as cancer might not be completely validated. Finally, information on significant risk factors for bladder cancer (such as cigarette smoking, race/ethnicity, or a history of urinary tract diseases) is sometimes missing, and information on some other risk factors (such as occupational or environmental exposure to carcinogenic chemicals) is rarely available. As a result, potential confounders sometimes cannot be adjusted for, resulting in a biased estimation of the associated risk.

5 Systematic Reviews and Meta-Analyses

In the study of rare events, meta-analyses are a useful way to increase statistical power by pooling risk estimations from different studies. However, one should keep in mind that study biases are reflected in meta-analysis results, and that a better level of evidence is reached when meta-analyses include randomized controlled trials rather than observational studies.

In December 2011, revaluation of pioglitazone by the EMA revealed the results of an unpublished meta-analysis conducted by the manufacturer, using its clinical trial database. Thirty-six trials were included, involving 22,000 patients (the PROactive study was analyzed separately). The study duration was less than 1 year for 24 studies, between 1 and 2 years for six studies, and more than 2 years for six studies. Including all cases of bladder cancer, even those that happened within 1 year of treatment, there were 19 cases in the pioglitazone group (0.15 %) versus 7 in the comparator group (0.07 %), resulting in an HR of 2.64 (95 % CI 1.11–6.31, $p = 0.029$). This risk was not significant when cases occurring within the first year of treatment were excluded [6]. In June and July 2012, two systematic reviews of published studies regarding the association between pioglitazone therapy and bladder cancer were published. At the time of their implementation, publications from the UK General Practice Research Database (GPRD) [49, 50] and The Health Improvement Network (THIN) [51] were not available. The first meta-analysis by Zhu et al. included a clinical trial and observational studies together [52]. Five studies were selected: the PROactive randomized trial [39], the Kaiser Permanente Northern California (KPNC) study by Lewis et al. [53], the French study by Neumann et al. [54] and two Taiwanese studies [55, 56], including 2,350,908 diabetic patients in total. The overall pooled RR was 1.17 (95 % CI 1.03–1.32). The RR for a cumulative treatment duration of >24 months and a cumulative dose of >28,000 mg were

Table 1 Characteristics of observational studies investigating the risk of bladder cancer associated with pioglitazone use

Authors	Year, Reference	Data source	Funding	Study design	Type of comparison	Time period	Study population	Bladder cancer definition	Exposure assessment	Adjusted confounding factors
Piccinni et al.	2011, [48]	FDA AERS database	Independent	Case/non-case study	Not applicable	Jan 2004–Dec 2009	37,841 reports concerning pioglitazone	Relevant Preferred Terms of MedDRA® classification[a]	Drug names referred to pioglitazone-containing medicines	Age, sex, other glucose-lowering drugs
Oliveria et al.	2008, [70]	US pharmacy claims database	Unknown	Retrospective cohort	Use of TZD vs other diabetes medications	Jan 2000–Dec 2004	191,223 diabetic patients, ≥18 years old, no bladder cancer within 12 months prior to follow-up	Hospital diagnoses and treatment received	Ever used, median duration of follow-up 3.9 years	Age, sex, schistosomiasis, pelvic radiation
Lewis et al.	2011, [53] 2012, [71]	Californian healthcare system (KPNC), USA	Takeda Pharmaceuticals	Prospective cohort	Use of pioglitazone vs other diabetes medications or dietary therapy	Jan 1997–Apr 2008 Jan 1997–Dec 2010	193,099 diabetic patients, ≥40 years old, no prior bladder cancer or none within 6 months of entry date Pioglitazone: 30,173 Comparators: 162,926	Inpatient and outpatient medical diagnoses	New users (8 % were exposed within 4 months of entry into the cohort), median exposure 2 years	Age, race, sex, other glucose-lowering drugs, socioeconomic status, smoking, occupational exposure, urinary diseases or symptoms, HbA_{1C}, duration of diabetes in the cohort, comorbidities
Neumann et al.	2011, [54]	SNIIRAM	Afssaps	Retrospective cohort	Use of pioglitazone vs other diabetes medications	Dec 2006–Dec 2009	1,491,060 diabetic patients (at least 1 prescription for a glucose-lowering drug in 2006), 40 to 79 years, no prior bladder cancer or none within 6 months of entry date Pioglitazone: 155,535 Comparators: 1,335,525	Hospital discharge diagnosis (ICD-10) and specific therapeutic procedure	Prevalent and new users, median exposure 1.5 years	Age, sex, other glucose-lowering drugs, proxy for disease duration
Li et al.	2012, [50]	Primary care medical record database (GPRD), UK	Unfunded	Retrospective cohort (matched with propensity score)	Use of pioglitazone vs other diabetes medications	Jan 2001–Dec 2010	207,714 diabetic patients, ≥40 years old, no prior bladder cancer or none within 90 days of entry date Pioglitazone: 23,548 Comparators: 184,166	Primary care medical record	New users, median follow-up 3.5 years	Age, sex, other glucose-lowering drugs, duration of diabetes, smoking status, body mass index
Tseng et al.	2012, [56]	Taiwanese National Health Insurance	Taiwanese National Health Research Institutes	Retrospective cohort	Use of pioglitazone vs other diabetes medications	Jan 2006–Dec 2009	54,928 diabetic patients Pioglitazone: 2,545 Comparators: 52,383	Reimbursement records (ICD-9)	Prevalent and previous users	Age, other glucose-lowering drugs, diabetes duration, comorbidities
Mamtani et al.	2012, [51]	Primary care medical record database (THIN), UK	US National Institutes of Health	Retrospective cohort	Use of pioglitazone vs rosiglitazone Use of TZD vs SU	Jul 2000–Aug 2010	Pioglitazone: 10,900 Rosiglitazone: 17,614 TZD: 18,459 SU: 41,396	Primary care medical record (Read codes)	New users	Age, sex, other glucose-lowering drugs, smoking, diabetes duration, recurrent urinary tract infections, body mass index, HbA_{1c}, comorbidities

Table 1 continued

Authors	Year, Reference	Data source	Funding	Study design	Type of comparison	Time period	Study population	Bladder cancer definition	Exposure assessment	Adjusted confounding factors
Chang et al.	2012, [55]	Taiwanese National Health Insurance	Taiwan Department of Health	Nested case–control study	Use of pioglitazone vs other diabetes medications	Jan 2000–Dec 2007	606,583 diabetic patients (497,663 prevalent and 108,920 newly diagnosed type 2 diabetes), ≥30 years old, no prior bladder cancer Cases: 1,583 Controls: 6,308	Linkage through National Cancer Registry	New users, median follow-up 7.9 years, mean cumulative duration 375 days	Matched for age, sex, duration of follow-up, glucose-lowering treatment duration for newly diagnosed type 2 diabetes patients; adjusted for socioeconomic status, diabetes complications, comorbidities, other glucose-lowering drugs
Azoulay et al.	2012, [49]	Primary care medical record database (GPRD), UK	Canadian Institutes of Health	Nested case–control study	Ever used pioglitazone vs other diabetes medications (excluding any thiazolidinedione)	Jan 1988–Dec 2009	115,727 diabetic patients (first ever oral glucose-lowering agent), ≥40 years old, no prior bladder cancer or none within 12 months of entry date Cases: 376 Controls: 6,699	Primary care medical record (Read codes)	New users, median exposure (for controls) 2.2 years	Matched for year of birth, year of cohort entry, sex, duration of follow-up; adjusted for HbA_{1c}, excessive alcohol use, obesity, smoking, previous cancer, previous bladder conditions, ever used other glucose-lowering drugs
Unknown	2011, [6]	Primary care medical record database (GPRD), UK	Takeda Pharmaceuticals	Nested case–control study	Use of pioglitazone vs comparators	Jan 1997–Dec 2010	Cases: 456 Controls: 1,884	Not available	Not available	Smoking

AERS Adverse Event Reporting System, *Afssaps* Agence Française de Sécurité Sanitaire des Produits de Santé [French Agency for the Safety of Health Products], *FDA* US Food and Drug Administration, *GPRD* General Practice Research Database, *ICD* International Classification of Diseases, *KPNC* Kaiser Permanente Northern California, *SNIIRAM* Système National d'Information Inter-régimes de l'Assurance Maladie [French National Health Insurance Information System]; *SU* sulfonylureas; *THIN* The Health Improvement Network, *TZD* thiazolininediones

[a] MedDRA® (Medical Dictionary for Regulatory Activities) terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) on behalf of the ICH

Table 2 Risk estimations for bladder cancer associated with pioglitazone use in observational studies

Authors	Year, Reference	No. of bladder cancers; incidence rate		Assessment of dose and duration	Risk ratio estimates (95 % CI)	RR for men (95 % CI)	Comments
Piccinni et al.	2011, [48]	31 reports of bladder cancer concerning pioglitazone		Not available	ROR: 4.30 (2.82–6.52)	Not available	ROR cannot be interpreted as RR; probable reporting bias; limited notoriety bias: significant relation in 2004 before publication of the PROactive study (year-by-year analysis)
Oliveria et al.	2008, [70]	Overall: $n = 178$		Not available	TZD: 1.05 (0.71–1.54) TZD combined with other oral glucose-lowering drugs: 1.92 (0.89-4.13)	Not available	Pioglitazone use was not analyzed separately; smoking status, occupational exposure, history of urinary pathology, duration of diabetes and prior use of glucose-lowering agents were not taken into account as confounders; potential information bias due to study of automated claims data; probable lack of statistical power
Lewis et al.	2011, [53]	Pioglitazone: 90; 81.5/100,000 PY	Comparators: 791; 68.8/100,000 PY	Ever used vs never used Duration of therapy >24 months Cumulative dose >28,000 mg	1.2 (0.9–1.5) 1.4 (1.03–2.0) 1.4 (0.96–2.1)	1.1 (0.9–1.5) 1.6 (1.2–2.3) 1.8 (1.2–2.6)	Few prevalent users at entry date: limited confounding by previous exposure; restricted to a localized region in the USA (unknown representativeness); substantial loss of follow-up rate; poor adjustment for duration of diabetes; nested case–control study data collected for smoking suggested no confounding effect
Lewis et al.	2012, [71]	Pioglitazone: 137	Comparators: 952	Ever used vs never used Duration of therapy >48 months Cumulative dose >35,000 mg	1.07 (0.87–1.30) 1.38 (0.97–1.96) 1.25 (0.91–1.74)	1.02 (0.82–1.27) 1.41 (0.96–2.06) 1.43 (1.03–1.99)	Changes in method for measurement of exposure duration not fully detailed nor explained; significantly increased risks observed in the subgroup of non-smokers with high exposure
Neumann et al.	2011, [54]	Pioglitazone: 175; 49.4/100,000 PY	Comparators: 1,841; 42.8/100,000 PY	Ever used vs never used Duration of therapy >24 months Cumulative dose >28,000 mg	1.22 (1.05–1.43) 1.36 (1.04–1.79 1.75 (1.22–2.50)	1.28 (1.09–1.51) 1.44 (1.09–1.91) 1.88 (1.30–2.71)	Large sample size and good population representativeness; high prevalent users rate (>60 %), 38,925 (25.0 %) filled a prescription for pioglitazone in January 2006 and 59,296 (38.1 %) during the first 6 months of 2006; patients >79 years old not included; poor adjustment for duration of diabetes; no adjustment for smoking

Table 2 continued

Authors	Year, Reference	No. of bladder cancers; incidence rate		Assessment of dose and duration	Risk ratio estimates (95 % CI)	RR for men (95 % CI)	Comments
Li et al.	2012, [50]	Pioglitazone: 66; 80.2/100,000 PY	Comparators: 803; 81.8/100,000 PY	Ever used vs never used	1.16 (0.83–1.62)	Not available	No analysis of cumulative exposure (analysis of follow-up time only); probable lack of statistical power
				Follow-up time >24 months	1.20 (0.74–1.93)		
Tseng et al.	2012, [56]	Pioglitazone: 10; 105/100,000 PY	Comparators: 155; 79/100,000 PY	Ever used vs never used	1.31 (0.66–2.58)	Not available	All bladder cancer in ever users occurred within a duration of therapy <24 months; Asian population; probable lack of statistical power; no adjustment for biochemical data, obesity, smoking, lifestyle, diet, occupational exposure, genetic parameters
Mamtani et al.	2012, [51]	Pioglitazone: 41; 123.8/100,000 PY	Rosiglitazone: 86; 106.6/100,000 PY	Ever used vs never used	1.14 (0.79–1.66)	Not available	Comparison of pioglitazone users vs SU users was not performed; authors concluded that there was a TZD class effect
				>5 years of use	1.59 (0.74–3.43)		
		TZD: 60	SU: 137	Ever used vs never used	TZD: 0.93 (0.68–1.29)	Not available	
				>5 years of use	TZD: 3.25 (1.08–9.71)		
Chang et al.	2012, [55]	Not available		Ever used vs never used	0.95 (0.70–1.29)	Not available	New users only: no confounding by previous exposure; no adjustment for family history of cancer or smoking
				Cumulative duration ≥3 years	1.56 (0.51–4.74)		
Azoulay et al.	2012, [49]	Overall in the cohort: 470; 89.4/100,000 PY		Ever used	1.83 (1.10–3.05)	Not available	New users only: no confounding by previous exposure; comparison between pioglitazone and rosiglitazone users suggested no confounding by diabetes severity
				Duration of therapy >24 months	1.99 (1.14–3.45)		
				Cumulative dose >28,000 mg	2.54 (1.05–6.14)		
				Ever used pioglitazone and rosiglitazone	0.78 (0.18–3.29)		
Unknown	2011, [6]	Not available		Ever used	1.33 (0.88–2.00)	Not available	Not peer reviewed; too little information available; probable lack of statistical power

CI confidence interval, *PROactive* PROspective pioglitAzone Clinical Trial In macroVascular Events, *PY* person-years, *ROR* reporting odds ratio, *RR* risk ratio, *SU* sulfonylureas, *TZD* thiazolinediones

1.38 (95 % CI 1.12–1.70) and 1.58 (95 % CI 1.12–2.06), respectively. It is worth noting that the numbers of cases from the PROactive study that were taken into account in this review were incorrect (14 as opposed to 5). The second meta-analysis, conducted by Colmers et al., studied the risk of bladder cancer associated with both pioglitazone and rosiglitazone [57]. Three cohort studies were selected for the pioglitazone meta-analysis: Lewis et al. [53], Neumann et al. [54] and Tseng [56]. The risk of bladder cancer was significantly increased with use of pioglitazone (pooled RR 1.22, 95 % CI 1.07–1.39). In contrast, the specific meta-analysis of rosiglitazone did not show any significant association with bladder cancer. The principal investigator of this study, cited in a subsequent comment, stated that a re-run of the meta-analysis of the bladder cancer risk with pioglitazone use, including the GPRD nested case–control study by Azoulay et al. [49], found a pooled RR increase from 1.22 to 1.26 [58]. In January 2013, two other meta-analyses found a similar overall risk for pioglitazone: the RR was 1.20 (95 % CI 1.07–1.34) according to Bosetti et al., who included six observational studies in their meta-analysis [59], and the HR was 1.23 (95 % CI 1.09–1.39) according to Ferwana et al., who included six observational or experimental studies in their meta-analysis [60].

6 Regulatory Management of the Bladder Cancer Risk

At the time of the first authorization of pioglitazone in the US, a key point for risk management was the information and recommendations included in the drug label regarding the occurrence of bladder cancer in male rats in preclinical studies. In 1999, the label information stated that "Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). The relationship of these findings in male rats to humans is unclear" [10]. It is worth noting that this last sentence was anecdotally removed during a label revision in June 2003. In 2000, for European authorization, data on animal carcinogenesis were also added to the 'Preclinical Safety' section of the Summary of Product Characteristics. In both cases, no recommendation for prescribers has been made, especially with regard to the selection and monitoring of patients potentially at risk.

At that time, regulators asked for implementation of a post-marketing surveillance study to monitor treated patients [6], and the KPNC cohort study was planned to start in 2003 and continue for a duration of 10 years. Since then, and during the following decade, minor changes have appeared in the product information, but no regulatory decision or recommendations were clearly stated.

In July 2004, the following sentence was added to the FDA label precautions section: "Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPARα/γ activity; however, Actos is a selective agonist for PPARγ." [61] This last statement was inappropriate, as the pharmacological profile of pioglitazone appears to be comparable to that of the dual PPARα/γ agonists [38]. This part was removed from the drug label in August 2006.

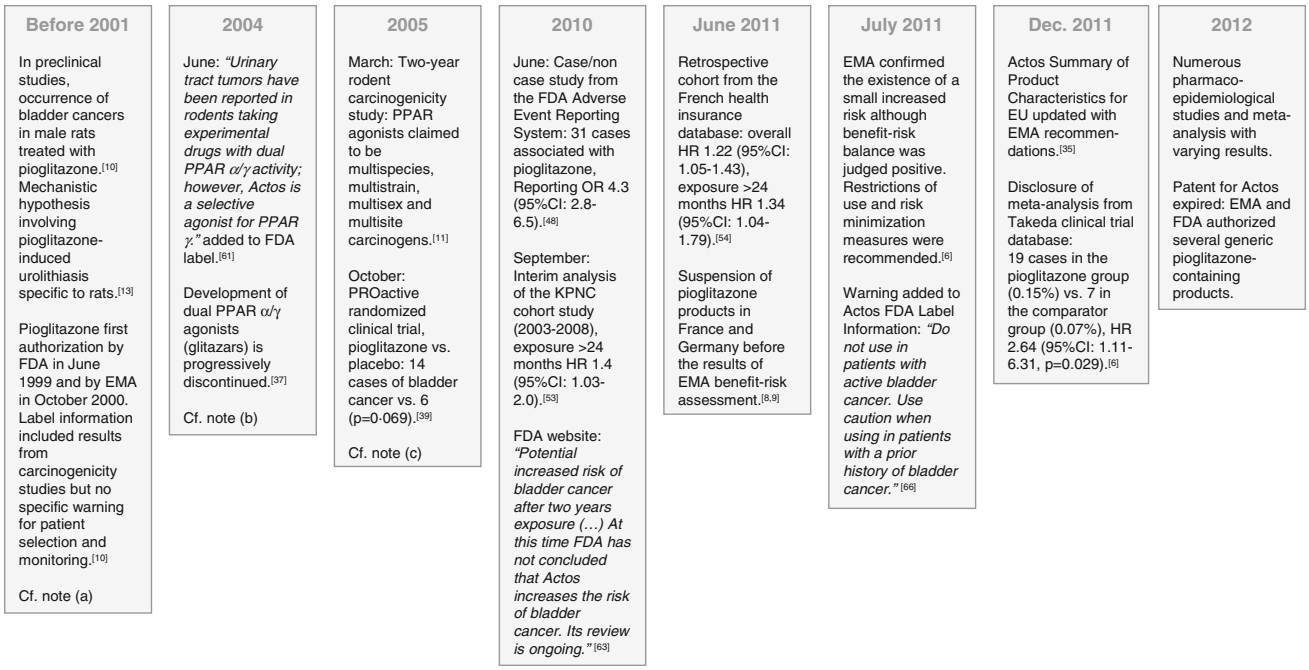
In September 2009, under a requirement of the FDA, a Risk Evaluation and Mitigation Strategy (REMS) was implemented for pioglitazone products in the USA. A medication guide was dispensed with each prescription, noting that "bladder cancer occurred in a few more people who were taking pioglitazone than in people who were taking other diabetes medicines. There were too few cases to know if the bladder cancer was related to pioglitazone" [62].

In September 2010, after the publication of the third interim analysis of the KPNC cohort study (from 2003 to 2008), the FDA issued an alert on its website mentioning a "potential increased risk of bladder cancer after two years exposure. At this time FDA has not concluded that Actos increases the risk of bladder cancer. Its review is ongoing" [63].

In April 2011, the European Commission asked the EMA Committee for Medicinal Products for Human Use (CHMP) to assess the impact of the available information on the risk-benefit balance for pioglitazone products. In June 2011, following the results of the retrospective cohort study from the Système National d'Information Inter-régimes de l'Assurance Maladie (SNIIRAM) [the French National Health Insurance Information System], Afssaps decided to suspend use of medications containing pioglitazone in France [8]. Soon after, the Federal Institute for Drugs and Medical Devices of Germany (BfArM) confirmed similar action [9].

In July 2011, the CHMP confirmed the existence of a small increased risk of bladder cancer associated with the use of pioglitazone but "could not identify any of the currently approved indications, where the benefits would specifically no longer outweigh the risks" [6]. The CHMP recommended that the following restrictions of use be added to the product information in order to ensure that the risk-benefit of pioglitazone remains positive:

- The adequacy of the response to treatment (e.g. reduction in HbA_{1c}) should be reviewed 3–6 months after initiation of therapy, and pioglitazone should be discontinued failing adequate response.
- Physicians should start treatment with the lowest available dose.



(a) In March 2011, specificity to rat will be contradicted in an animal study: acid-forming diet did not reduce the incidence of hyperplasia associated with pioglitazone.[18]
(b) In March 2012, it was reported that pioglitazone pharmacological profile was comparable to that of the PPAR α/γ agonists.[38]
(c) In October 2011, recalculated RR with the true number (5) in the placebo group was 2.83 (95%CI: 1.02–7.85, p=0.040).[45]

CI: Confidence Interval; EMA: European Medicines Agency; EU: European Union; FDA: US Food and Drug Administration; HR: Hazard Ratio; OR: Odds Ratio; PPAR: Peroxisome Proliferator-Activated Receptors; RR: Risk Ratio.

Fig. 1 Timeline for main scientific information and regulatory actions about pioglitazone and bladder cancers

- Use of pioglitazone is contraindicated in patients with current bladder cancer, a history of bladder cancer or uninvestigated macroscopic haematuria.
- Macroscopic haematuria should be investigated before starting pioglitazone therapy.
- Patients should promptly report macroscopic haematuria or other symptoms such as dysuria or urinary urgency.
- Combined use of pioglitazone with insulin should be considered with caution in elderly patients.
- The risk of bladder cancer has been added to the table of adverse reactions, under the header "Neoplasms benign, malignant and unspecified (including cysts and polyps)" with the frequency "uncommon" being listed for all indications [6].

In addition, risk minimization measures such as educational materials, a prescriber guide, a 'Dear Healthcare Professional Communication' letter and an update of the risk management plan were implemented. The CHMP also concluded that "systematic bladder cancer screening for monitoring purposes was considered as unrealistic". Finally, further analyses, including a pan-European epidemiological study, were requested by the CHMP [6].

These conclusions were made public in July 2011 and, on its website, the EMA has recommended "new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer" [64] but has stated that its "positive benefit-risk balance is confirmed as second and third line treatment" [65].

In July 2011, the following warning was added to the pioglitazone US label information: "Preclinical and clinical trial data, and results from an observational study suggest an increased risk of bladder cancer in pioglitazone users. The observational data further suggest that the risk increases with duration of use. Do not use in patients with active bladder cancer. Use caution when using in patients with a prior history of bladder cancer" [66].

In December 2011, the Actos Summary of Product Characteristics for the EU was updated with the CHMP recommendations [35].

Figure 1 presents a summary timeline of the scientific evidence and regulatory management.

7 Comments and Perspectives

The burden of type 2 diabetes mellitus is massive and still growing, and diabetic patients are expected to number 30 million by 2030 [67]. In 2011, sales for Actos totalled $3.4 billion in the USA [68]. The patent for Actos expired in 2012, and numerous generic products are entering the market. Whatever the fate of pioglitazone will be in the

future, we can point to several comments about different aspects of this matter.

7.1 Should Pioglitazone Have Been Licensed in the First Place?

In terms of benefit for patients, we can legitimately question whether authorization of pioglitazone was worth it after all. In 1999, we knew from the premarketing data that pioglitazone showed a mild reduction in HbA_{1c} and, except for frequent fluid retention, it had a relatively acceptable tolerance profile. Pioglitazone was authorized on the assumption that results from a surrogate endpoint such as HbA_{1c}, compared with placebo, would transform into benefits in terms of cardiovascular morbidity and mortality. It appears that this assumption was wrong. No evidence has proven that tight HbA_{1c} control really reduces the risk of death from a cardiovascular event [69]. More than 10 years after its initial marketing, no well-designed long-term study has yet strictly confirmed the real benefit of pioglitazone in reducing the incidence of cardiovascular disease. It is another example of the well known—but unfortunately often forgotten—difference in drug evaluation between clinically significant endpoints, such as morbidity/mortality or quality-of-life, and surrogate biological endpoints, such as HbA_{1c}.

7.2 A Modest But Critical Risk of Bladder Cancer

It would be neither ethical nor practical to implement a randomized control trial to definitively answer the question regarding the risk of bladder cancer. Although some studies, such as the study by Azoulay et al. [49], have achieved optimal standards, it is obvious that no observational study would equal the level of proof provided by a randomized controlled trial. However, evidence can be provided by the combination of different data from different fields and different study designs, so the increased risk of bladder cancer associated with pioglitazone seems real to us. The observational studies analyzed in this article indicate that the basal risk of bladder cancer in diabetic patients is estimated at 50–100/100,000 person-years, which corresponds to less than 1 case per 1,000 patients per year. Risk estimates for pioglitazone do not seem, at first glance, to represent a significant impact in terms of public health. Moreover, the majority of cases associated with pioglitazone use have showed low-grade lesions [6]. However, this risk must not be overlooked. Firstly, the dramatic increase in the prevalence of diabetes over the last 25 years and its projection into the future suggest that a small risk of serious adverse events associated with a popular 'blockbuster' will consequently affect an extensive population of patients. Given the worldwide exposure to pioglitazone, which is estimated to exceed 20 million patient-years in 2011 [6], the risk ratio, which ranges from 1.2 to 2.6 (according to the overall effects found in meta-analyses) could hypothetically represent approximately 2,000–18,000 additional bladder cancer cases. Secondly—notwithstanding an a priori low lethality—bladder cancer still represents a consequent deterioration of the quality of life of affected patients. Finally, this risk seems mainly avoidable without a great loss of opportunity for patients and society. Indeed, the real benefit of pioglitazone in reducing cardiovascular disease or total mortality has not been proven; its real cost effectiveness has not been comparatively assessed; and alternative glucose-lowering drugs are available.

7.3 Lost Opportunities for Risk Management

It seems clear that before the authorization of pioglitazone, premarketing data raised doubt about the risk of bladder cancer associated with the drug. Even if the bladder cancers that occurred in male rats treated with pioglitazone were claimed at that time to be specific to rats, a strict precautionary approach would have led to a delay in authorization until in-depth evaluation of this risk had been performed. A less strict approach could have been to at least advise prescribers to closely monitor their patients, with this potential risk in mind. None of these approaches were chosen. In 2005, by excluding the benign tumour that occurred in the placebo group, a correct analysis of the PROactive data would have revealed a significant association between pioglitazone use and bladder cancer in a randomized trial, and would have strengthened the existing doubt [45]. Another inaccuracy lies in the definition of pioglitazone as a selective agonist for PPARγ: it now appears that pioglitazone has a pharmacological profile similar to that of the dual PPARα/γ agonists, which were discontinued before 2006 because of safety concerns, including bladder tumours [37, 38]. Whatever the cause of these inaccuracies may be, the opportunity was lost to provide regulators with correct and timely information to properly assess the safety profile of pioglitazone. It took until 2011 for the pharmacoepidemiological data to be sufficiently numerous and conclusive to initiate the application of safety measures such as prescription restrictions, close monitoring and review of the adequacy of the response to treatment. The first lesson we can draw from this sequence of events is that if the opportunity to implement regulatory action to prevent potential side effects before drug authorization is missed, it takes many years to make changes once a drug has been marketed. Secondly, it is crucial to be particularly vigilant with the safety information provided before and after marketing. In a context of weak efficacy, the doubt must always benefit the patient.

7.4 The Difficulty of Screening and Monitoring Treated Patients

In the example of pioglitazone, the great difficulty lies in identifying the patients who are at greater risk of developing bladder cancer. Cystoscopy associated with biopsy is the examination of choice to detect bladder cancer, but it is totally unfeasible as systematic screening for bladder lesions in order to select or monitor pioglitazone-treated patients. Recommendations to not accumulate known and detectable risk factors for the prescribing of pioglitazone and to clinically monitor treated patients have been implemented but only represent an approach by default. In other words, patient history and clinical urinary symptoms including macroscopic haematuria, which are the criteria now recommended for selection and monitoring of patients, may be insufficiently reliable to avoid exposure of patients at risk. Pioglitazone may be useful in the population of patients with a good response and good tolerance, but it appears that practitioners cannot really count on HbA_{1c} to assess its cardiovascular effectiveness and cannot count on restricted prescribing to ensure its safety. This problematic situation is now left in the hands of prescribers, who may consequently encounter complex patient management with medico-legal responsibility.

8 Conclusions

The pioglitazone example gives us a good opportunity to think about how the drug regulatory system works. With new therapeutic agents in development in the field of diabetes, as in other therapeutic fields, this complex situation will happen again, and risk management will have to be more proactive. As a basis for reflection, some solutions can be proposed:

- Do not overlook basic pharmacological (i.e. pharmacokinetic and pharmacodynamic) studies, and strictly analyze the slightest doubt.
- Do not authorize drugs without well-designed, long-term studies comparing clinical outcomes with those of reference medications, not just placebo.
- Always ensure that the results of any study are disclosed, and widely spread the available information to the medical community and the public.
- Promptly conduct post-marketing studies (clinical trials and observational studies) with the highest level of proof to assess the safety, effectiveness and cost effectiveness of newly marketed drugs, and ensure that these studies are independent from pharmaceutical firms.
- If a risk of serious adverse event is suspected, immediately implement strict and reliable recommendations for prescription and monitoring.
- Suspend any drug whose risk-benefit balance is judged to be negative and, in cases of doubt, make decisions only in the patient's best interests.

In our opinion, any improvement implies an increasing role of health authorities and academic organizations. No solution would satisfy everyone involved (health authorities, the pharmaceutical industry, the clinical community and patients), but we must think about patients first and give ourselves the means to comply with the principal precept of medical ethics: "primum non nocere".

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