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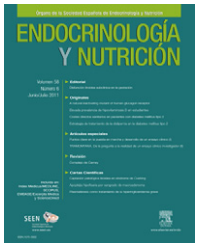

EDITORIAL

The new antidiabetic agents in the firing line... safety reasons or witch hunt?☆

Los nuevos antidiabéticos en el punto de mira... ¿razones de seguridad o caza de brujas?

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Since the controversy raised by rosiglitazone, which ended in September 2010 with its withdrawal from the market by the European Medicines Agency (EMEA), antidiabetic drugs recently introduced on the market or those pending approval have been in the firing line. They are closely evaluated and their risk-benefit balance is questioned at the slightest evidence of any adverse effect.[1–3]

It can, therefore, be stated that a sort of witch hunt is now underway. This is on the one hand beneficial, as it has forced pharmaceutical companies to design increasingly stringent clinical trials and with objectives that are based not only on improvements in laboratory parameters but also on clinical results.

However, on the other hand, it should not be forgotten that type 2 diabetes mellitus (DM2) currently affects approximately 350 million people worldwide with resulting associated morbidity and mortality, and that it is necessary to develop new, more potent and safer antidiabetic drugs, in order to control this pandemic and reduce its comorbidity.[4]

In fact, as far back as December 2008, the U.S. Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee agreed that, to ensure benefit from a new antidiabetic drug, the responsible pharmaceutical company had to demonstrate that the treatment in question did not compromise cardiovascular safety. For this, it recommended that the design of phase II and III clinical trials has cardiovascular endpoints of a sufficient duration (at least 2 years) and includes patients at high risk of suffering cardiovascular events. In addition, the upper range of its confidence interval (CI) was limited to 1.8 for preapproval studies and to 1.3 for postmarketing studies.[5]

However, conducting these trials was a more complicated task. In an editorial, Bloomgarden explained the reasons for the difficulty in evaluating the cardiovascular safety of antidiabetic drugs.[6] If only patients with high cardiovascular risk were included, the recruitment numbers would be feasible, but newly diagnosed patients would be the ones who would benefit from stricter glycemic control and, therefore, they were the ones who should be evaluated. Because the annual event rate in this group would be around 0.5%, it would require a 4 times larger sample, as well as a longer trial duration, making its design very difficult due to its high cost.[6] The same reasoning and difficulties can be applied to other adverse effects currently ''pursuing'' antidiabetic drugs such as tumors.

In the next section we will examine the current situation.

Antidiabetic drugs and tumors

Pioglitazone

After the withdrawal of rosiglitazone, an increase was expected in prescriptions for the other available

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thiazolindinedione and pioglitazone (PIO), so confirmation of its safety profile became a key objective. Although its beneficial effects at the cardiovascular level had been demonstrated, its potential association with an increased risk of bladder tumors was a serious negative factor.[7,8]

Although most in vitro trials have shown that peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists are able to induce apoptosis in a significant number of cells lines and inhibit the proliferation of cancerous cells in colon and breast tumors,[9] toxicity studies revealed an increase in bladder tumors with PIO. In these preclinical studies, male rats treated with PIO developed more bladder tumors than those treated with placebo. The association could not be demonstrated in female rats or mice, and these results were attributed to an adverse species effect.[11] In addition, subsequent investigations noted that this risk could be modified with a diet change, suggesting a mechanism related to the anatomy of the bladder and the accumulation of acid in the urine of these animals.[12] However, due to these results and the detection of PPAR-γ in healthy uroepithelial tissue and bladder tumors, in 2003 the FDA requested Takeda Pharmaceuticals to design a safety study to resolve these discrepancies, with the result that an observational study with a duration of 10 years was designed. Since then, many articles have been published with conflicting results.

Koro et al. published the first epidemiological study of this nature in 2007.Its aim was to evaluate the risk of colon, breast and prostate tumors among patients treated with thiazolindinediones versus other antidiabetic drugs, using an American database (Integrated Healthcare Information Services) and including 126,971 subjects with DM2. No difference was found among patients with DM2 treated with either rosiglitazone or PIO compared to the other drugs.[13] In that same year, Govindajaran et al. published a retrospective analysis whose aim was to evaluate the impact of the thiazolindinediones on the incidence of cancer in subjects with DM2. This showed a reduction in cases of pulmonary tumors in patients treated with this group of drugs.[14] However, it should be stressed that in both studies the two thiazolindinediones were analyzed together and the risk of bladder cancer was not evaluated.[13]

Although it was not one of its objectives, in the PROactive study 20 cases of bladder tumors were diagnosed in a total of 5238 patients with DM2; of these, 11 tumors were ruled out since they had been diagnosed in the first year of randomization, this exposure time being too short for them to be attributable to a causal relationship. Of the remaining 9 cases, 6 and 3 cases corresponded to groups treated with PIO and placebo, respectively; 4 cases from the first group and 2 from the second group had known risk factors for bladder tumors (smoking, exposure to carcinogenic substances, family or personal history of bladder cancer and/or repeated genitourinary infections). Therefore, it was considered unlikely that the cause of these tumors was PIO.[7]

In June 2011, the FDA, the EMEA, and the Spanish Agency for Medicinal Products and Medical Devices (AEMPS) warned about a possible increased risk of bladder tumors in patients treated with PIO based on the results obtained from an internal analysis of a 10-year epidemiological study to evaluate the safety of PIO with regard to bladder tumors, and another retrospective study conducted in France.[15,16]

The interim analysis of the epidemiological study conducted by Takeda Pharmaceuticals at the request of the FDA included 193,099 subjects with DM2 from a registry of diabetic patients in Northern California (Kaiser Permanent Northern California Registry). To be enrolled in the study, patients had to have a minimum drug exposure of 6 months and those with a personal history of bladder cancer were excluded. Of the 30,173 patients treated with PIO, 90 cases of bladder cancer were diagnosed versus 791 cases of the 162,926 patients in the other group. Although the use of PIO was not associated with an increased overall risk of bladder cancer with a hazard ratio (HR) of 1.2 (95% confidence interval [CI] 0.9–1.5), an increased risk of bladder malignancy was found among patients with exposure to the drug greater than 24 months (HR 1.4 [95% CI 1.3–2.0]). Of these, 95% were diagnosed in the early stages. One of the limitations of the study was the impossibility of determining the existence of other risk factors for bladder cancer in these patients.[15] However, using the same database, two months earlier an article had been published in which the relationship between PIO and the 10 most common tumors (prostate, breast, lung, endometrium, colon, non-Hodgkin's lymphoma, pancreas, kidney, rectum and melanoma) was studied. After adjusting for possible confounding factors, only in individuals treated with PIO could a trend be shown to melanoma (HR 1.3; 95% CI 0.9–2) and non-Hodgkin's lymphoma (HR 1.3; 95% CI 1–1.8) and, interestingly, to a decreased risk of bladder cancer (HR 0.7; 95% CI 0.4–1.1).[10]

In June 2011, another study was published using as an information source the FDA's adverse event registry from 2004 to 2009, where 93 cases of bladder tumors were recorded. A significantly higher risk of bladder tumor was observed with PIO (odds ratio (OR) 4.30; 95% CI 2.82–6.52). Although a clear awareness bias might be suspected, this relationship was already known to be significant in 2004 before publication of the PROactive study.[17]

The contradictory results of the above studies, their heterogeneity, their failure to consider proven risk factors for bladder tumor (smoking, exposure to carcinogens, etc.) that may have falsely increased the number of cases, the short exposure to the drug for a neoformative process to be induced, their failure to consider the exposure time and dose, etc., have led to the different regulatory authorities, except in France, deciding to wait for more conclusive results before taking drastic decisions. At present, their use is not currently recommended in DM2 patients with a history of bladder cancer or when symptoms and/or signs suggesting bladder cancer appear in patients treated with PIO.[18,19]

Sodium–glucose cotransporter type 2 inhibitors (SGLT2Is)

Recently, the FDA expert panel voted against the approval of dapaglifozine, the first SGLT2I having concluded its clinical development phase. Although the final decision has yet to be taken, this first vote threatens this new class of antidiabetic drugs. The reason was a sign of a potential increase in the risk of developing breast and bladder tumors. Nine cases of bladder cancer were seen among 5478 patients (0.16%) and 9 cases of breast cancer among 2223 women (0.4%). Data

for the placebo arms included one case of bladder cancer among 3156 patients (0.03%) and one case of breast cancer among 1053 women (0.09%). These differences were not statistically significant; however, they were sufficient to persuade the FDA to carry out a deeper review of the available data. Some experts justify the differences by a diagnostic bias, since SGLT2Is increase urinary infections. This could have precipitated the diagnosis of bladder tumors. In addition, half the samples were diagnosed between 6 and 12 months after the start of the trials and were sufficiently advanced to call into question the involvement of dapagliflozine in their development. Similarly, weight loss occurring in the treatment arms could have facilitated the detection of mammary nodes. In this regard, this effect has also been described with regard to some medicines for the treatment of obesity.[20]

Liraglutide and GLP-1 analogs in general

Liraglutide, like the other approved glucagon-like-peptide-1 (GLP-1) agonist, exenatide, was rapidly accepted and has been used by DM2 professionals since its approval by regulatory agencies.[21] This is due to the significant improvement in the metabolic parameters (glycosylated hemoglobin, baseline and prandial blood sugar levels, systolic blood pressure, lipid profile and natriuretic peptide), well as a significant weight reduction. If we add a low incidence of hypoglycemia, a potential preservation/regeneration of the pancreatic beta cell mass, and a good tolerability (mild gastrointestinal type adverse events that decrease with a gradual dose titration and usually disappear over time), this makes them a promising group of drugs.[22–24]

However, doubts arose when preclinical studies conducted in rodents showed a significant increase in calcitonin levels (a very sensitive and specific marker of the proliferation of parafollicular C cells) as well as a significantly greater risk of C cell hyperplasia (CCH) and medullary thyroid carcinoma (MTC).[25,26]

The presence of GLP-1 receptors has been demonstrated in rodent C cells. It has also been found that GPL-1 and its analogs (liraglutide, exenatide, taspoglutide and lixisenatide) stimulate calcitonin (CT) secretion by these cells and that it is inhibited with the GPL-1 receptor antagonist, exendin-4. In rodents, continuous stimulation may result in C cell hyperplasia, parafollicular cell adenomas and also carcinomas. It is known that in these species the GLP-1-CT axis plays an essential role in calcium homeostasis.[27] However, it should be noted that the dosages of liraglutide used were up to 8 times higher than the maximum recommended doses in humans and that rats are susceptible to spontaneous alterations in C cells.[26]

However, no increase in CT or C cell proliferation has been shown in primates exposed to doses of liraglutide up to 64 times the maximum used in humans. Liraglutide has not been shown to stimulate CT secretion in human cell lines, and there are fewer GLP-1 receptors in the human thyroid.[26]

The Liraglutide Term and Action on Diabetes (LEAD) phase III trials found that 1.3% of individuals treated with liraglutide at doses of 1.8 mg/day showed an increase in plasma CT levels, a percentage slightly higher compared to control animals, but always within normal ranges. In addition, 4 cases of C cell hyperplasia were reported in patients with DM2 treated with liraglutide versus 1 case in the comparator treatment group (1.3 versus 0.6 cases per 1000 patient-years). During follow-up, 2 cases of MTC were diagnosed, both in the comparator group. It should be noted that 4 of these patients treated with liraglutide had high baseline CT levels.[28]

In addition, it should be taken into account that, depending on the test method used, up to 10% of the general population has CT levels above 10 ng/L, particularly if they are males, elderly persons and/or smokers. Proton pump inhibitors cause a false increase in CT, and it is not known if the subjects with the highest CT levels in the LEAD trials were those treated with drugs from this group who had been randomized to the highest dose of liraglutide and, presumably, the worst tolerated at the gastrointestinal level. In any case, CT in all patients treated with liraglutide in the LEAD trials were always lower than 20 ng/L (the cut-off point from which it is recommended to extend the study with a stimulation test).[21,28]

It should be noted that CCH is a premalignant lesion in patients with multiple endocrine neoplasia type 2 (MEN-2), but this has not been shown in individuals with no mutations in the RET oncogene or family MTC. In fact, the prevalence of CCH may be as high as 30% in biopsies or autopsies performed in the general population.[29]

Using more than 5000 patients enrolled in the LEAD trials, a study was published in March 2011 in which CT plasma concentrations were determined quarterly for a period of 2 years. In this study, mean baseline CT levels were within the lower limit of normal in all treatment groups and remained in this range throughout the follow-up. Mean increases during follow-up were higher with liraglutide at doses of 1.8 mg/day ($p = 0.0472$) and 1.2 mg/day ($p = 0.04$) when compared to placebo, but were not greater when compared to active comparators. No significant differences were shown between liraglutide and exenatide. During follow-up, 6 cases of C-cell disease were diagnosed, 4 patients were treated with liraglutide (0.11%) and 2 were in the active comparator group (0.14%).[30] However, and as in other studies, the short exposure time to the drugs and follow-up together with the few cases with diagnosed C-cell disease make it difficult to decide on the safety or harmfulness of GLP-1 analogs in humans.

Thus, the FDA has included this potential adverse effect in the summary of product characteristics and has established as a contraindication the use of liraglutide in patients with a family or personal history of MTC or MEN-2. To try to resolve these unknowns, the FDA has established a registry of tumors in patients treated with GPL-1 analogs to monitor the annual incidence of MTC for the next 15 years, since due to the low incidence of MTC it would be impossible to design a clinical trial with an adequate statistical power.[31]

On the other hand, routine screening of MTC is not recommended in patients treated with liraglutide or GLP-1 analogs because, in general, the high number of thyroid incidentalomas would lead to unnecessary examinations.[31]

But nevertheless...

There is clear evidence that some types of tumors are more prevalent among diabetics, particularly those with DM2.

Since it was reported as a casual finding in 1932, many studies have shown an increased risk of pancreas, liver, endometrial, breast, colon, rectum, and bladder cancer. In contrast, there is a lower risk of prostate cancer.[32,33]

As potential mechanisms, insulin resistance, hyperinsulinism, and increased insulin-like growth factor-1 (IGF-1) levels in these individuals have been suggested, thus promoting tumor growth.[34] In addition, there is clinical evidence that the prevalence of DM2 in individuals newly diagnosed with any type of cancer is from 8% to 18%, thus suggesting a bidirectional association.[32]

In addition, at the present time the protective effect of metformin would appear to be undeniable. Many epidemiological studies have shown that treatment with metformin alone decreases the risk of developing cancer as compared to other hypoglycemiant treatments, and this effect appears to be independent of its hypoglycemic effect.[32] A meta-analysis published in 2010 including epidemiological studies demonstrated up to a 31% relative risk reduction of the incidence of cancer and death related to this disease in subjects with DM2 treated with metformin versus other oral antidiabetics.[35] The Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) study, the first prospective observational study, showed a dose-dependent reduction in mortality associated with cancer in DM2 patients treated with metformin.[36]

When forming an opinion, it should not be forgotten that not only have the newest hypoglycemic treatments been ''suspected'', but such traditional and widely used drugs as sulfonylureas (SU) and even insulin itself have also been accused of increasing the risk of cancer, suggesting endogenous or exogenous hyperinsulinism as a possible cause.[32,34,37]

A retrospective epidemiological study published in 2006 including 10,309 subjects with DM2 treated with metformin, SU or insulin monotherapy showed that mortality due to cancer during a mean follow-up of 5.4 ± 1.9 years was 4.9% (162/3340) in patients treated with SU, 3.5% (245/6969) in patients treated with metformin and 5.8% (84/1443) in patients treated with insulin. After adjusting for different factors, the cohort of patients treated with SU had increased mortality associated with cancer as compared to the metformin group (HR 1.3 [95% CI 1.1–1.6]; $p = 0.0012$). This risk was greater in the insulin-dependent group (HR 1.9 [95% CI 1.5–2.4]; $p < 0.0001$). However, one of the most important limitations of this study was the lack of clinical data, such as blood glucose control, body mass index, or smoking, which may have biased the results.[37]

Possibly, the risk of cancer is not the same for all SUs, a group of highly heterogeneous drugs that make generalizing conclusions impossible. For example, Monami et al. reported that mortality associated with cancer was significantly higher in patients treated with glibenclamide than in those treated with gliclazide.[38]

Nor does glycemic control appear to increase or reduce the risk of cancer or worsen its prognosis.[34]

However, it is stressed that the potential risk or benefit of the different hypoglycemic agents in terms of the greater or lesser risk of cancer should be established on the basis of randomized clinical trials.

On the other hand, we should remember that the leading cause of death of our patients with DM2 is cardiovascular disease with a 2–4 fold higher risk compared to nondiabetic subjects, and that this is the main cause of the reduction in life expectancy of about 8 years less than the general population in an individual aged 40 years recently diagnosed with DM2.[7]

Incretins and pancreatic disease

Drug-induced pancreatitis is an uncommon condition, but its actual incidence is difficult to establish, as this is an exclusion diagnosis. Cases of pancreatitis have been published with up to 500 different drugs, including agents commonly indicated in DM2, such as statins, angiotensin-converting enzyme inhibitors, glibenclamide and, more recently, with therapies based on the incretin system.[39] However, the causal relationship is difficult to establish, because an up to 3 times higher risk of pancreatitis has been shown in DM2, increasing this risk to up to 5 times higher in the DM2 group aged 18–44 years.[40] In addition, a large number of comorbidities associated with DM2 (hypertriglyceridemia, obesity, smoking) are themselves risk factors for pancreatitis.[41] Therefore, it is difficult to establish if the increased risk of pancreatitis is due to the treatment of DM2 itself, to other frequently associated metabolic disorders or whether the cause is iatrogenic.

After the publication of the first case of pancreatitis secondary to treatment with exenatide in 2006,[42] new cases of pancreatitis were reported which had presumably been caused by this drug. As a result, the different regulatory drug agencies added pancreatitis as a possible adverse effect in the summary of product characteristics. Since then many articles have been published with conflicting results.[43–45]

In February 2011, an observational study in which 25,719 subjects with DM2 treated with exenatide were included versus 234,536 subjects with DM2 treated with other antidiabetics found 40 cases of pancreatitis among users of exenatide and 254 cases in the comparator group. Although the exenatide group had a higher body mass index and were treated with a greater number of hyperglycemic drugs, the relative risk for pancreatitis was comparable to the other group (RR 0.2 [95% CI 0.0–1.4]). It should be noted that this study was supported by the company Amylin Pharmaceuticals.[43]

Elashoff et al. published another article with completely opposite results. Using the FDA's adverse effects database from 2004 to 2009, they showed a risk of pancreatitis up to 6 times higher in patients treated with exenatide (OR 10.68 [95% CI 7.75–15.1; $p < 10^{-16}$]). Likewise, the risk of pancreatic cancer was 2.9 times higher in patients treated with exenatide ($p = 9 \times 10^{-5}$). As in any epidemiological study, its retrospective nature, the potential awareness bias and the lack of clinical information are limitations which must be taken into consideration when interpreting the results.[45] To date, no clinical study has been performed with the objective of determining the risk of pancreatic malignancies in patients treated with exenatide. Such a study could only be compared with an analysis by the Commission of Drugs of the German Medical Association in which 11 cases of pancreatic carcinoma were identified, an unusually large number compared to other hypoglycemic agents. Nevertheless, because of the short time between taking the drug and the appearance of cancer, it is impossible that it itself could have

caused the tumors, and a more plausible hypothesis is that it acted as an accelerator of the process.[46]

However, preclinical toxicity studies show no gross abnormalities suggesting pancreatitis in rodent necropsies, although a single study showed that daily dosing with 10 mcg/kg of exendina-4 for 75 days (doses much higher than those used in humans) in Sprague-Dawley rats induced acinar inflammation, chronic pancreatitis and elevated serum lipase.[47] A possible explanation for this disagreement is that exenatide causes low level pancreatic inflammation that cannot be shown clinically or macroscropically.[48]

Regarding the increased risk of pancreatitis with the use of liraglutide, the incidence of this entity was evaluated in the phase III LEAD trials. Seven cases of pancreatitis were diagnosed among the 4257 patients randomized to liraglutide compared to only 1 case among the 2381 patients in the comparator group (2.2 cases versus 0.6 cases per 1000 patient-years). This represents a 4:1 ratio in favor of liraglutide predisposing to the development of acute pancreatic inflammation. The small numbers involved makes the drawing of conclusions difficult, but taking into account these numbers and the history of its predecessor exenatide, the FDA has required epidemiological postmarketing studies and animal studies to resolve these questions.[23]

Following the marketing of the first dipeptydyl peptidase-4 inhibitor (DPP-4), sitagliptin, and as happened with exenatide, cases of pancreatitis appeared that were attributed to the use of this drug. In preclinical studies, except for 1 isolated case of histological pancreatitis in a model of transgenic diabetic rats, no relationship between the administration of sitagliptin and the development of pancreatitis has been demonstrated, despite the exposure of these animals to higher doses than those used in humans.[49,50]

Subsequently, Merck studied the possible relationship between sitagliptin and pancreatitis. An analysis of 19 clinical trials including approximately 10,000 patients with DM2 revealed no evidence of an increased risk of pancreatitis in the sitagliptin treated group versus the comparator group (0.08 cases per 100 patient-years versus 0.1 cases per 100 patient-years),[50] but it should not be forgotten that the study sponsor was the manufacturer of the molecule and that most of the studies included in the metaanalysis were sponsored by the pharmaceutical industry.

The article by Elashoff et al., evaluated the risk of pancreatitis and pancreatic malignancies not only with exenatide, but also with sitagliptin. The risk of pancreatitis was 6 times higher in the sitagliptin treated group (OR 6.74 [95% CI 4.71–10; $p < 10^{-16}$]) and there was a 2.7 times higher risk of pancreatic malignancies in this group ($p = 0.008$).[45] It is worth mentioning that it has been shown that sitagliptin may induce a pancreatic metaplasia of ductal cells, a known premalignant lesion, in some animal models, and that this effect is suppressed with metformin coadministration.[50]

With regard to another DPP-4 inhibitor, vildagliptin, so far preclinical and clinical studies have not shown an increase in pancreatic disease.[51] There is only one case of pancreatitis in the literature attributed to this drug.[52] Nor have pancreatic disorders been found with saxagliptin. However, it has only recently been put on the market.

Restrictions on postmarketing studies, the potential increased risk of pancreatitis in patients with DM2, and possible interference with the results of metformin, often associated with this class of drugs, may interfere with establishing if there is actually a greater risk of pancreatic disease with incretin therapies. In addition, it will be difficult to obtain these answers from randomized clinical trials since the low incidence of events reduces their statistical power. It is possible that longer-term preclinical and epidemiological studies may be required.

Infections and DPP-4 inhibitors

The ubiquity of the DPP-4 enzyme has led to the question being raised of whether its inhibition would have adverse effects. Since it is found on the surface of the cells that participate in the immune response, it was suspected that they could have an immunomodulatory effect during the continued suppression of the enzyme.[53]

During the preapproval clinical trials of the different molecules, more upper airway infections, nasopharyngitis and mild infections in general were documented in all groups treated with DPP-4 inhibitors than in the comparator group. The mechanism involved is not clear, but does not appear to be due to an impairment in the activation of CD4+ T-lymphocytes.[54]

In contrast, pooled studies showed no statistically significant differences in terms of more infections in patients treated with vildagliptin or saxagliptin compared to the reference group.[51,55] Also, and in the same way as in pancreatitis, some epidemiological studies have suggested that patients with DM2 may have a higher susceptibility to developing mild infections, secondary to dysfunctions in the immune system. However, the results of these studies are contradictory. Consequently, regulatory drug agencies required after authorization of these drugs that these questions be resolved by safety studies.[53]

Recently, using Vigibase, the World Health Organization's database for adverse drug effects, 8083 adverse effects were found and analyzed in patients treated with DPP-4 inhibitor monotherapy (out of a total of 106,469 adverse effects related to hypoglycemic agents). Infections documented in the group treated with inhibitors DPP-4 were two times more prevalent compared to metformin (OR 2.3 [95% CI 1.9–2.7]), particularly upper airway infections (OR 12.3 [95% CI 8.6–17.5]).[53] Despite the above-mentioned limitations on the use of a database as an information source, and until publication of the results of ongoing clinical trials, it should be considered in our standard clinical practice. In addition, the infections were always mild, so that possibly in most cases the benefit of glycemic control outweighs this possible adverse effect. Nevertheless, the effects of chronic inhibition of the DPP-4 enzyme on the immune system should be monitored.

Points to consider...

Most hyperglycemic therapies are under suspicion, and except metformin virtually no molecule is there as a conclusive evidence of a favorable risk-benefit ratio in clinically

relevant objectives including reduced complications, survival, etc.

There are data which suggest a possible increased risk of bladder cancer with pioglitazone, breast and bladder cancer with SGLT2Is, and medullary carcinoma of the thyroid and pancreas with drugs based on the incretin pathway. Similarly, some results indicate that the latter are associated with an increased risk of pancreatitis. A higher risk of infections with the DPP-4 inhibitors has also been reported. However, as we have seen, these clinical signs are often inconsistent and may be subject to important diagnostic or reporting biases, especially in those based on postmarketing studies and pharmacovigilance systems.

Although the disclosure of data based on exploratory analyses can identify ''signs'' of potential risks for the patient, publication should be serious and its degree of evidence should be stressed by the media. Thus, it would be desirable to require standardized reporting rules to confirm the degree of evidence provided by the different publications. In recent years, we have seen reports of observations on safety that have not been adequately validated. Similarly, we have seen that results of observational studies have had equal or even greater resonance, both in the scientific press and in the general media, than the robust data derived from well-designed clinical trials. This ''bad press'' has probably harmed the field of diabetes, both for patients and for professionals and the industry.

It should be remembered that the optimization of glycemic control decreases the risk of developing microvascular and macrovascular complications, and that these are the leading causes of morbidity and mortality in diabetic patients. Therefore, we need to have new hyperglycemic therapies whose benefits on glycemic control are not outweighed by unacceptable adverse effects. In addition, the low incidence of events, particularly for malignancies, will make it difficult to obtain definitive answers from clinical trials that are hardly feasible because they must enroll a very high number of patients and have a very long duration.

Meanwhile, here are some recommendations which, if adopted, could enable us to move forward:

The design of preclinical and early human trials should include objectives that are reproducible and based on the biology of the systems.

Large long-term clinical trials should be designed with sufficient power to answer such questions as cardiovascular safety or the risk of malignancies. It is said that the conduct of these types of studies will increase the cost of drug development and, therefore, will lower investment in the field of diabetes. However, FDA data suggest that since their standards have become stricter, the number of assessment requests rather than decreasing has increased.[56] On the other hand, the design of multifactorial studies evaluating multiple interventions and multiple responses could involve different sponsors and be more feasible economically.

Meanwhile, some simple steps may improve our ability to analyze the data obtained from the trials that are soon to be started. For example, with regard to bladder cancer, to exclude patients with microhematuria at the start of the study and to monitor urine tests more frequently; with regard to breast tumors, to require mammography at the start and during the study for phase 3 of the seven STLG2I drugs that are currently in phase 2 of their clinical development.

Another step would be to facilitate the transfer of information between the different pharmacovigilance systems. There are 366 million people with diabetes. Countries with large populations such as China or India will probably have a greater capacity for identifying risks. The possibility of consulting the databases of other countries would allow regulatory agencies to distinguish casual findings from real safety problems more reliably.

The liberalization of access to data from clinical trials would promote the dissemination of the results of the studies whether or not they are published.

Finally, other possible initiatives would be the epidemiological monitoring of patients included in phase 3 clinical trials and the conduct of postmarketing megatrials worldwide, some of which, in the area of cardiovascular safety, are already ongoing.

Conflicts of interest

Dr. Masmiquel has been paid for talks or consultancy by Abbott, GSK, MSD, Lilly, Menarini, Novartis, Pfizer, NovoNordisk, Sanofi-Aventis, and Roche. Dr. Masmiquel has participated in clinical trials sponsored by Novartis, Lilly, Abbott, Boehringer-Ingelheim, MSD, and Astra-Zeneca.

Dr. Nicolau has been paid for talks by MSD, Lilly, Novartis, Ferrer, NovoNordisk, Sanofi-Aventis, and Almirall. Dr. Nicolau has participated in clinical trials sponsored by NovoNordisk, Novartis, Lilly, Boehringer-Ingelheim, and Astra-Zeneca.

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