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Safety considerations in the use of glucagon-like peptide-1 receptor agonists

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ABSTRACT

A great variety of medications are currently available for the treatment of type 2 diabetes mellitus. Therefore, determining the efficacy and safety of these medications must be a priority for choosing the appropriate treatment for each patient. Glucagon-like peptide-1 receptor agonists are a relatively new and attractive option for type 2 diabetes mellitus treatment due to their capacity for reducing glycated hemoglobin A1c, weight loss, and low risk of hypoglycemia. Recently, some safety warnings have been published. Therefore, the purpose of this review is to objectively analyze the available information about the safety and tolerability of the different glucagon-like peptide-1 receptor agonists. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:82-91)

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Key words: Glucagon-like peptide-1 receptor agonist. Adverse event. Safety. Tolerability.

RESUMEN

Hoy en día existe una gran variedad de medicamentos disponibles para el tratamiento de la diabetes *mellitus* de tipo 2 (DM2), por lo que conocer su eficacia y seguridad debería ser prioritario para la elección del tratamiento adecuado para cada paciente. Los agonistas del receptor del péptido parecido al glucagón tipo 1 (aRGLP-1) son una opción atractiva y relativamente nueva para el tratamiento de la DM2 debido a su capacidad para reducir la hemoglobina glicada A1c, conseguir pérdida de peso y el bajo riesgo para producir hipoglucemia. Recientemente han sido publicadas algunas advertencias sobre la seguridad de su uso, por lo que el propósito de esta revisión es analizar de manera objetiva la información disponible sobre la seguridad y tolerabilidad de los diferentes aRGLP-1.

Palabras clave: Glucagón tipo 1 (aRGLP-1). Agonistas del receptor. Eventos adversos. Seguridad. Tolerabilidad

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INTRODUCTION

Choosing the best therapy for patients with type 2 diabetes mellitus (T2DM) is complicated. The choice must be based on its capacity to reduce glycated hemoglobin A1c (HbA1c), patient preferences, adverse events, risk of hypoglycemia, weight increase, and cost[1].

In regard to the algorithm of the American Diabetes Association and the European Association for the Study of Diabetes published in 2012[2], it is suggested that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) could be used as an adjunct dual or triple therapy with metformin or other agents. The American Association of Clinical Endocrinologists in 2013[3] proposed a treatment algorithm where GLP-1 RAs were highly ranked in the hierarchy of usage, even as monotherapy when metformin is contraindicated or not tolerated. The main reason for recommending GLP-1 RAs over other medications is due to their capacity to produce weight loss and their low hypoglycemic risk, along with some cardiovascular protection[4-6].

Glucagon-like peptide-1 (GLP-1) receptors are expressed in different tissues such as pancreas, intestine, kidney, lung, thyroid, and brain, which could mediate some non-glucose effects, but this wide distribution may also produce different adverse effects[7]. In this review, safety would refer to the potential medical risk posed by a drug, and tolerability pertains to adverse effects as they affect patient acceptability of therapy[8].

The aim of this review is provide in-depth information to the medical community regarding the safety and tolerability of GLP-1 RAs, along with offering physicians the capacity to explain all the benefits and risks of prescribing this kind of therapy.

SAFETY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Hypoglycemia

Hypoglycemia is the most important limiting factor in the pharmacologic treatment of T2DM; therefore, diabetes treatment agents that minimize hypoglycemia have aroused great interest[9].

Native GLP-1 stimulates insulin secretion in the presence of hyperglycemia and does not interfere with the counter-regulatory glucagon response to hypoglycemia[10]. The GLP-1 RAs have demonstrated similar glucose-dependent effects, which explains the relatively low risk of hypoglycemia with their use[11]. The incidence of hypoglycemia depends mainly on the GLP-1 RAs and on the underlying therapy[10].

A relative risk of mild hypoglycemia is demonstrated when GLP-1 RAs are used as monotherapy compared with placebo[8]. A 24-week monotherapy study of exenatide (5-10 µg twice daily) in treatment-naive patients with type 2 diabetes yielded a 4-5% incidence of mild hypoglycemia compared with 1% for placebo, without major hypoglycemic episodes[12]. Another study was carried out where liraglutide 1.8 mg vs. exenatide 10 µg was compared and demonstrated significantly fewer episodes of mild hypoglycemia with liraglutide compared with those using exenatide (1.9 vs. 2.6 events/patient-year; rate ratio 0.55; 95% CI: 0.34-0.88; p = 0.0131)[13].

The combination of GLP-1 RAs and metformin has not been associated with an increase in the rate or severity of hypoglycemic events[14-16]. The combinations most often associated with hypoglycemia are GLP-1 RAs with sulfonylureas or with insulin[17,18].

The glucose-dependent insulinotropic action of GLP-1 RAs could be an effective option for patients who experience inadequate glycemic control with oral anti-diabetic agents and who need to intensify treatment with a relatively low risk of hypoglycemia. It is necessary to evaluate the underlying therapy of patients, for example, the use of sulfonylureas or insulin analogues, to consider a reduction of the concomitant therapy dose.

Use in kidney and liver disease

Preclinical studies indicated that exenatide is cleared via glomerular filtration and is the reason for the poor tolerance in patients with advanced renal disease[19]. The Food and Drug Administration (FDA)

recently requested a post-marketing report of renal impairment in association with the drug. Between April 2005 and October 2008 the agency received 78 reports of altered renal function in patients taking exenatide, sixty-two cases represented acute renal failure and 16 cases of renal insufficiency. Due to the above information, exenatide is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease (need for dialysis)[20].

Liraglutide is degraded by proteolysis; therefore, renal impairment or hepatic insufficiency has little effect on liraglutide pharmacokinetics[21,22]. The European Union prescribing information points that no dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance 60-90 and 30-59 ml/min, respectively). There is little therapeutic experience in patients with severe renal impairment (creatinine clearance < 30 ml/min). For this reason, liraglutide cannot currently be recommended for use in patients with severe renal impairment, including patients with end-stage renal disease[23,24]. Unlike the U.S. recommendations in regard to exenatide, labeling of liraglutide only indicates caution in regard to its use in patients with renal or hepatic impairment[23].

No current data are available in regard to renal damage with the use of lixisenatide. However, it is known that its clearance is predominantly through glomerular filtration with subsequent proteolytic degradation. For this reason, patients must be followed closely as with exenatide[25].

Despite the cases reported of acute renal failure in patients with T2DM treated with GLP-1 RAs, recent studies have associated GLP-1 RAs with renoprotective properties. In animal models, administration of GLP-1 RAs reduced systemic hypertension and albuminuria and therefore ameliorated renal damage. These data were histologically verified[26-28].

Allergy, antibody formation, and injection-site reactions

The GLP-1 RAs are therapeutic peptides. Therefore, there is concern with regard to the development of antidrug antibodies[29]. Induction of an immune response is a well-known effect of protein-based drugs, which occurs less frequently with agents with more similarity to endogenous human proteins[30]. Exenatide is derived from a non-mammalian source and has a homology of 53% with human GLP-1[31], whereas liraglutide is based on the structure of human GLP-1, sharing a 97% amino acid sequence homology to the native protein[32]. This difference in homology with human GLP-1 could explain the lower incidence of antibody formation with liraglutide compared with exenatide.

Large clinical trials reported that 27-49% of patients treated with twice-daily exenatide developed drug antibodies[12,33]. The rate of antibody formation is higher with once-weekly exenatide, occurring in 74% of patients[33]. Antibodies to liraglutide, the GLP-1 RA with the highest homology with human GLP-1, were detected in only 4-13% of patients[34-35]. The greatest concern in regard to developing antidrug antibodies is that this could lead to a decreased efficacy of the medication or to an increase in hypersensitivity reactions over time[35].

Exenatide administered once weekly commonly causes a small lump at the injection site shortly after injection due to its microsphere formulation, which disappears within 3-4 weeks[36]. Severe anaphylactic reactions with GLP-1 RAs have not been reported in clinical trials; however, post-marketing reports show that anaphylactic reactions rarely occur with liraglutide (≥ 1/10,000 to < 1/1,000), very rarely with exenatide (< 1/10,000) and uncommonly with lixisenatide (≥ 1/1,000 to < 1/1,00)[37-40].

Injection-site reactions, such as rash, erythema, or itching, are common with GLP-1 RAs. In phase II and III trials, 5.1% of patients receiving exenatide twice daily, 16% of patients receiving exenatide once weekly, and 3.9% of patients receiving lixisenatide experienced injection-site reactions, which are transient and generally do not cause treatment discontinuation[37-40].

Musculoskeletal disorders

A meta-analysis of 16 randomized controlled trials (n = 11,206) assessed the risk of bone fractures

associated with GLP-1 RAs in comparison with placebo or other active drugs. Liraglutide was associated with a significantly decreased risk of incident bone fractures (OR: 0.38; 95% CI: 0.17-0.87), whereas exenatide was linked with an increased risk (OR: 2.09; 95% CI: 1.03-4.21)[41].

Despite the negative effects reported in the meta-analysis with exenatide, a clinical trial that included 69 metformin-treated subjects with T2DM randomized to exenatide twice daily or insulin glargine showed no significant changes in serum alkaline phosphatase and calcium and phosphate levels. Bone mineral density was also similar in both groups after 44 weeks of therapy[42,43].

Infection

The GLP-1 RAs have been related with the presence of infections such as nasopharyngitis, influenza, cystitis, and viral infections, but no cause-effect association has been established[37-40].

Cardiovascular system

In 2008 the FDA recommended that all drugs investigated for T2DM treatment should be evaluated to provide greater patient safety[44]. A meta-analysis of 33 clinical trials with exenatide twice daily, exenatide weekly, liraglutide, taspoglutide and albiglutide showed no increase in major cardiovascular events and all-cause mortality when compared with placebo or other medications[45].

In some clinical trials a small but persistent increase in heart rate (2-4 beats/min) has consistently been observed in patients treated with GLP-1 RAs[46-48]. This increase in heart rate appears to be due to the activation of the GLP-1 receptors expressed by sinoatrial node myocytes[49], but it is unknown if this has any clinical significance on cardiovascular outcomes.

However, these agents have not been on the market for a long period of time and there is a lack of long-term safety data on cardiovascular mortality and other long-term cardiovascular parameters[50]. Some of the studies being carried out to evaluate GLP-1 RA cardiovascular outcomes are EXSCEL (exenatide once weekly), LEADER (liraglutide), REWIND (dulaglutide), and HARMONY (albiglutide)[51-54]. One of the already concluded studies of cardiovascular outcomes is ELIXA, which was carried out with lixisenatide in patients with a recent acute coronary syndrome. Investigators concluded that in patients with T2DM and a recent acute coronary syndrome, the addition of lixisenatide to usual care did not significantly alter the rate of major cardiovascular events or other serious adverse events such as the presence of pancreatitis[55]. The LEADER study of cardiovascular outcomes with liraglutide is already complete; however, results are still unknown[24].

Pancreatitis

A retrospective epidemiological study from the USA showed a threefold increase in pancreatitis in patients with T2DM compared with the general population[56]. Known pancreatitis risk factors, such as obesity, biliary disease, hypertriglyceridemia, and use of sulfonylureas, are more common in patients with T2DM than in the general population[57,58].

Since U.S. approval of the use of exenatide from April 2005 until December 31, 2006, the FDA received 30 reports of acute pancreatitis in association with exenatide use, prompting the agency to request a new warning on the product label[59]. The FDA also received six reports of cases of hemorrhagic or necrotizing pancreatitis in patients taking exenatide in recent years. Analysis of the 30 individual pancreatitis cases reported to the FDA of patients treated with exenatide showed that 90% involved known contributory factors such as obesity, gallstones, alcohol use, and hypertriglyceridemia, making it difficult to determine the actual cause of the pancreatitis[60].

According to a meta-analysis realized with diverse clinical trials and cohorts where adverse events were reported to the Adverse Event Reporting System (AERS) database[61], which supports the FDA post-marketing pharmacovigilance, frequency of pancreatitis has been reported > 6-fold as an adverse event for patients administered exenatide

compared with other therapies for diabetes. Despite the fact that the AERS database can provide valuable information, it exhibits numerous and substantial limitations[62]. For this reason, further long-term pharmaco-epidemiological studies and clinical trials are necessary to prove if an association exists between pancreatitis and GLP-1 RAs.

Preclinical data show that GLP-1 receptors are expressed in exocrine pancreas cells, which have a proliferative capacity. This could result in an overgrowth, leading to partial obstruction, increased back pressure, and low-grade inflammation, which may result in the development of acute pancreatitis[63].

A study carried out to evaluate GLP-1 receptor activation by exenatide or liraglutide and the expression of some genes in the exocrine murine pancreas demonstrated that GLP-1 RAs do not predispose or exacerbate experimental pancreatitis in mice[64]. In studies carried out in mice, rats, and monkeys exposed to liraglutide for two years at levels up to 60-times higher than in humans, it was also concluded that liraglutide treatment did not induce pancreatitis in those animals[65].

A recent systematic review that included 60 studies was carried out to analyze the risk of pancreatitis associated with incretin treatment in subjects with T2DM. The analysis of the randomized trials did not suggest an increased risk of pancreatitis with incretins vs. control (OR 1.1; 95% CI: 0.57-2.17). Estimates by type of incretin suggested similar results (OR 1.05; 95% CI: 0.37-2.94) for GLP-1 RAs vs. control. A non-observational study analysis suggested an increased risk of pancreatitis associated with incretin therapy[61].

Because of the contradictory data regarding the relationship between GLP-1 RAs and risk of acute pancreatitis due to the presence of other contributing factors usually present in patients with T2DM, the FDA is continuously evaluating data for a better understanding of this safety issue and also urges both patients and healthcare professionals to report adverse events[59,60].

As cited above, the ELIXA study had the objective of rating cardiovascular events or other serious adverse events after the administration of lixisenatide during ~ 25 months to 6,068 patients with T2DM. Investigators found that lixisenatide was not associated with a higher rate of serious adverse events or severe hypoglycemia, pancreatitis, pancreatic neoplasms, or allergic reactions when compared with placebo[54].

New studies being carried out with other GLP-1 RAs will probably show similar results. Both the FDA and the European Medicines Agency will potentially establish less stringent warnings about the use of GLP-1 RAs and the relation with the development of pancreatitis. The most recent documented data have not provided compelling evidence for increased risk of pancreatitis or pancreatic cancer[66].

Cancer

Glucagon-like peptide-1 seems to have much wider effects on the function and survival of cells that express its receptor. *In vivo* studies have demonstrated that insulin-gene transcription is stimulated, whereas cell apoptosis is inhibited by GLP-1 receptor activation and even stimulates cell growth, raising the issue of whether activation of the GLP-1 receptor pathway might have positive (i.e. restoration of the functional b-cell mass) or negative (i.e. inducing proliferation of premalignant lesions) effects when chronically used for the treatment of T2DM[67-69].

An important aspect when analyzing whether specific antidiabetic agents, such as metformin, insulin, and GLP-1 RAs, increase the development of neoplasms is that considerable epidemiological evidence supports that T2DM itself represents a high risk for the development of certain types of cancer[70,71].

The main tissues where concerns are indicated in regard to the trophic effects of GLP-1 and its potential carcinogenic properties are pancreas and thyroid. Recent studies, however, also demonstrated that GLP-1 RAs could have beneficial properties on colon, breast, and prostate cancer[69].

Pancreas

The same molecular mechanism previously described to explain a possible link between GLP-1

RAs and acute pancreatitis could theoretically lead to the development of pancreatic cancer. In a study carried out by Elashoff, et al. where the AERS was analyzed, it was reported that pancreatic cancer was 2.9-fold higher in patients using exenatide than in patients exposed to other therapies[72].

Eleven studies on pancreatic cancer associated with exenatide reported to the Drug Commission of the German Medical Association were recently analyzed. Exposure to exenatide was relatively short (2-33 months). Thus, there is considerable doubt that the cases were related to the medication. The time between tumor induction, tumor development, and metastasis/clinical diagnosis was ~ 10 years[73].

A study carried out where pancreatic tissue from organ donors with T2DM taking sitagliptin (n = 7), exenatide (n = 1) or other medications (n = 12) and from a non-diabetic subject group (n = 14) found that 40% of patients treated with incretin-mimetic drugs had an increased pancreatic mass. Moreover, patients receiving incretin-mimetic drugs had a-cell hyperplasia and glucagon-expressing micro-adenomas (3/8) and one had a neuroendocrine tumor[74]. This study is insufficient to draw conclusions as only one of the studied patients was receiving a GLP-1 RA[75].

A meta-analysis of 25 studies showed that the use of exenatide (OR 0.86; 95% CI: 0.29-2.60) and liraglutide (OR 1.35; 95% CI: 0.70-2.59) did not significantly increase the risk of pancreatic cancer, independently of the baseline comparison[76].

A study carried out using human pancreatic cancer cell lines showed that these express the GLP-1 receptor, but the findings have been inconsistent as to whether GLP-1 RAs may have pro-oncogenic characteristics[77]. Another group of investigators was unable to detect GLP-1 receptors in 21 human pancreatic adenocarcinomas, which suggests that GLP-1 receptor expression may be restricted to cell lines[78].

The ELIXA study did not find any differences in regard to the presence of pancreatic neoplasms in 6,068 patients with T2DM who were followed for a median of 25 months when compared with placebo[55]. Similar findings are expected with the other GLP-1 RA long-term studies.

Thyroid

Concerns have also been expressed regarding a possible link between GLP-1 RAs and medullary thyroid cancer[72], which are based principally on rodent studies.

Liraglutide, exenatide, lixisenatide, and native GLP-1 have shown a potential to activate thyroid C-cell GLP-1 receptors and stimulate calcitonin release by the increase of calcitonin gene expression[78], which seems to be species-specific. In rodents, GLP-1 receptor density in thyroid C-cells is from 20- to 45-fold higher than that reported for humans and monkeys[78,79].

Liraglutide and exenatide have been associated with the development of thyroid C-cell tumors in rodents after lifetime exposure at supra-therapeutic doses[78]. During a 13-week continuous exposure to GLP-1 RAs, an increase in plasma calcitonin and C-cell hyperplasia was found in wild-type mice but not in GLP-1 receptor knockout mice[79]. Studies carried out with monkeys did not find an increase in calcitonin release or any effect on C-cell fraction in the thyroid gland after an 87-week intervention with liraglutide with a 60-fold higher dose than the highest dose recommended in humans[78].

Despite the hypothesis that only rodents are sensitive to developing thyroid cancer after exposure to GLP-1 RAs, one of the end-points of recent studies with GLP-1 RAs on humans is the increase in calcitonin release and other possible markers of thyroid carcinoma[80].

Some studies have recently challenged the hypothesis that normal human thyroid tissue does not express the GLP-1 receptor. In one study it was found that GLP-1 receptors are expressed in thyroid tissue of controls (5/15 cases) and in the thyroid of patients with C-cell hyperplasia (9/9 cases), papillary carcinoma (3/15 cases), and medullary carcinoma (11/12)[81].

Data obtained from different prospective clinical studies showed no increased calcitonin levels under

therapy with GLP-1 RAs in patients with T2DM[78,82]. In the AERS database the incidence rate of thyroid cancer in patients treated with exenatide was clearly higher compared with other control drugs[72].

In clinical trials only five cases of thyroid neoplasm were reported with exenatide twice daily and only three adverse thyroid-related events were reported with once-weekly exenatide[37,40].

In liraglutide-exposed patients, 12 serious adverse thyroid events were reported, which corresponds to 0.2% of treatment-exposed patients. Also, in all patients who participated in the liraglutide clinical trial programs, serum calcitonin concentrations were monitored as a biomarker for C-cell proliferation, and no increases were observed throughout the trials[39].

Treatment with lixisenatide during the clinical development program did not produce trends in the incidence of thyroid neoplasms in comparison to placebo or other comparison groups. Calcitonin levels also remained stable over time[38].

Across the phase III head-to-head studies among GLP-1 RAs, mean calcitonin levels were largely unchanged, and only one case of treatment-emergent thyroid cancer was observed (a papillary thyroid carcinoma in a patient with liraglutide in AWARD-6)[83]. Cases of medullary thyroid carcinoma have been reported in patients treated with liraglutide during the post-marketing period, although data are insufficient to establish or exclude a causal relationship[84].

Although evidence indicates that there is no relationship between GLP-1 RAs and thyroid cancer or hyperplasia, the longer-acting GLP-1 RAs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple neoplasia syndrome[29].

Other tissues

Unlike the effect of GLP-1 RAs on pancreatic and thyroid cancers, GLP-1 receptor activation by GLP-1 RAs is believed to inhibit tumor growth in two common cancers: colon and breast[68].

In a study carried out using CT26 murine colon cancer cell line, which expresses a GLP-1 receptor, exenatide inhibited proliferation and induced cell apoptosis and also reduced colony formation and enhanced irinotecan-induced apoptosis[85]. This was confirmed in an *in vivo* study where exenatide induced apoptosis of CT26 cells implanted into the flanks of mice[86].

Some data have also been published about the relationship between GLP-1 RAs and breast cancer. *In vitro* exposure to exenatide significantly reduced the number of colonies formed by MCF-7 (estrogen-receptor-positive) and MDA-MB-231 (estrogen-receptor-negative) cells, whereas noncancerous HB2 cells were not affected[87]. A possible mechanism of action of exenatide is that it induces p38 activation, which is related with growth inhibition or apoptosis[88]. However, the classic GLP-1 receptor has not been identified in breast cancer cells. Actions must thus be mediated through a not-yet identified alternative receptor.

TOLERABILITY OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

The GLP-1 RAs are generally well tolerated, with the most common side effects being gastrointestinal with mild and transient nausea[49,89]. The incidence of nausea seems to be higher with the short-acting agents, possibly because of fluctuations in plasma GLP-1 concentrations[90,91]. Nausea incidence has been observed to decrease over time with continued dosing for both short- and long-acting GLP-1 RAs[92,93].

Other common adverse gastrointestinal effects reported with the use of GLP-1 RAs are diarrhea and vomiting, but are less frequent with longer-acting formulations[84,94,95]. Over time, these are often self-limiting for some patients. Less than 5% discontinued GLP-1 RAs in clinical trials due to gastrointestinal effects, but higher rates of discontinuation (5-10%) are seen in clinical practice. These adverse effects could be reduced by a slow dose-titration[96,97].

In clinical trials, patients treated with once-weekly exenatide presented less nausea (25 vs. 35%) and

vomiting (11 vs. 19%) than patients treated with once-daily exenatide[98]. Phase III studies comparing once-daily liraglutide vs. once-weekly exenatide also found a lower incidence of nausea (9 vs. 20%) and vomiting (4 vs. 11%)[92]. In relation to short-acting GLP-1 RAs, phase III studies show a lower incidence of nausea and vomiting in patients treated with lixisenatide than with once-daily exenatide (25 vs. 35%, respectively)[97].

There are different mechanisms by which GLP-1 RAs could cause gastrointestinal symptoms. One of the principal mechanisms is that this medication slows gastric emptying, which decreases the velocity of the passage of nutrients through the gastrointestinal tract, inducing satiety and possibly nausea[99]. It is also possible that these effects could be mediated through the central nervous system. A study conducted in rats described that central administration of a GLP-1 induced some taste displeasures[98].

CONCLUSIONS

The decision to use any medication must always be based on efficacy, safety, and patient factors. Despite current evidence that the use of GLP-1 RAs is safe, long-term pharmaceutical studies will continue to evaluate cardiovascular and other adverse outcomes with their use. Evidence is still lacking due to the relatively short time that these medications have been on the market.

For this reason, all types of analyses performed during the post-marketing period, such as observational studies, reviews, and meta-analyses, are valuable for pharmacovigilance activities and to detect safety issues in a timely manner. Most safety-related drug problems emerge after market approval.

Despite the fact that many of the doubts related to the safety of GLP-1 RAs are being resolved and much of this information indicates that their use is safe, it is mandatory to continue to carry out these studies to develop a complete safety profile of GLP-1 RAs and to promptly detect any potential, yet unknown, risks.

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