Combined Analysis of Three Large Interventional Trials With Gliptins Indicates Increased Incidence of Acute Pancreatitis in Patients With Type 2 Diabetes

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Diabetes Care 2017;40:284–286 | DOI: 10.2337/dc15-1707

META-ANALYSIS

OBJECTIVE

Data on the possible relationship of gliptin treatment with the incidence of acute pancreatitis have been controversial. The aim of the current study was to combine data on the incidence of acute pancreatitis from three large randomized controlled trials.

RESEARCH DESIGN AND METHODS

Three trials designed to test cardiovascular safety and efficacy of add-on treatment with a gliptin were included in the analysis, as follows: SAVOR-TIMI 53 (saxagliptin), EXAMINE (alogliptin), and TECOS (sitagliptin). The trials included 18,238 gliptin-treated patients and 18,157 placebo-treated patients. Data were combined using a random-effects model meta-analysis.

RESULTS

The incidence of acute pancreatitis was significantly increased in the gliptin-treated patients when compared with the control groups (odds ratio 1.79 [95% CI 1.13–2.82], *P* = 0.013). The difference in the absolute risk was small (0.13%).

CONCLUSIONS

Treatment with gliptins significantly increased the risk for acute pancreatitis in a combined analysis of three large controlled randomized trials.

Dipeptidyl peptidase 4 inhibitors (gliptins) are incretin effect–enhancing oral antidiabetic drugs that have been used for a decade in the treatment of patients with type 2 diabetes. The important advantage of these drugs is related to the low incidence of hypoglycemia and lack of weight gain (1).

It has been suggested that the risk of acute pancreatitis (AP) may be increased with the use of gliptins (2–4), but the data have not been consistent (5,6). The reasons for this inconsistency might lie in different limitations of the previous studies. In the retrospective studies, the adjustment for all of the important confounders, such as risk factors for AP, was not possible or performed. The earlier clinical randomized trials predominantly did not have long enough exposure times, and the pancreatitis events were not adjudicated. Given the mentioned controversial results, a discussion about the possible risks of incretin-based treatments is ongoing in the medical literature, including in *Diabetes Care* (7,8).

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Received 3 August 2015 and accepted 29 December 2015.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

See accompanying articles, pp. 161 and 164.

The aim of the present analysis was to combine data from three recently published randomized trials that included a large number of subjects with type 2 diabetes, in which AP was a predefined adverse event and gliptin treatment continued for at least 18 months.

RESEARCH DESIGN AND METHODS

Three multicenter, randomized, double-blind, placebo-controlled cardiovascular (CV) outcome studies, which were designed to test CV safety and the efficacy of add-on treatment with a dipeptidyl peptidase 4 inhibitor, were included in the combined analysis, as follows: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) (9), Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (10), and Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) (11). The details of their designs can be found in the corresponding reports (9–11). Per the requirements of the U.S. Food and Drug Administration, the studies were intended to test the CV safety of gliptins.

During the studies, AP was also followed as a serious adverse event and was adjudicated by blinded independent adjudicating committees both in the SAVOR-TIMI 53 and TECOS trials (9,11). Within these two studies, the percentage of confirmed cases among reported AP cases was not significantly different between the treatment arms.

In all three studies, the investigators in both the gliptin and placebo arms were encouraged to give standard-of-care treatment of type 2 diabetes. Data on the incidence of AP were retrieved from the original reports (9–11).

For combining the data on the incidence of AP from all three trials, Comprehensive Meta-Analysis Software version 2 (Biostat, Englewood, NJ) was used. Data were combined using a random-effects model and were expressed as odds ratios (ORs) and 95% CIs. The I^2 statistic was calculated as a measure of heterogeneity among the included trials.

RESULTS

Results of the individual studies as well as the combined analysis are displayed in Fig. 1.

Study name	Pancreatitis / Total		Statistics for each study			
	Gliptin	Placebo	Odds ratio	Lower limit	Upper limit	p-Value
SAVOR	17 / 8280	9 / 8212	1.875	0.835	4.209	0.128
EXAMINE	12 / 2701	8 / 2679	1.490	0.608	3.651	0.383
TECOS	23 / 7257	12 / 7266	1.922	0.956	3.865	0.067
TOTAL	52 / 18238	29 / 18157	1.786	1.133	2.816	0.013

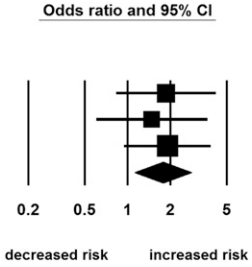

Figure 1—Combined analysis of the incidence of AP cases in the SAVOR-TIMI 53, EXAMINE, and TECOS studies.

In the SAVOR-TIMI 53 trial, adjudicated definite AP was reported in 0.21% of patients within the saxagliptin group and in 0.11% patients in the placebo arm. One severe case of AP was observed in the saxagliptin arm, and one case was observed in the placebo arm. No fatal event was observed in the saxagliptin arm, and one fatal event was reported in the placebo arm (9).

In the EXAMINE study, nonadjudicated AP was observed in 0.44% of patients in the alogliptin arm and in 0.30% patients in the placebo group. No fatal case was reported (10).

In the TECOS study, adjudicated AP was reported in 0.32% of patients in the sitagliptin arm and in 0.17% patients in the placebo group (11). While no severe case of AP was reported in the placebo arm, four cases of severe AP, including two fatal cases, were reported in the sitagliptin arm (12).

No heterogeneity among the published trials was observed (I^2 = 0). Although in each published study the OR for AP incidence in gliptin-treated patients was >1.0, the increase was not statistically significant in any single study. However, in the combined analysis of all three studies (Fig. 1) the overall incidence of AP was significantly increased in the gliptin-treated patients (OR 1.79 [95% CI 1.13–2.82], P = 0.013), which corresponded with an absolute increase of 0.13% in AP incidence. Not including the unadjudicated data from the EXAMINE study in the analysis had a minor effect on the statistical significance of the increased incidence of AP (OR 1.90 [95% CI 1.12–3.23], P = 0.017).

CONCLUSIONS

The combined analysis of the data from three large randomized trials comparing add-on gliptin treatment with placebo treatment showed a significant 79% relative increase in the incidence of AP in patients with type 2 diabetes with gliptin treatment.

Our results are in good accordance with a population-based matched case-control study (3) in which the authors were able to adjust for a number of confounders, such as hypertriglyceridemia, alcohol use, gallstones, tobacco abuse, biliary or pancreatic cancer, and cystic fibrosis, as well as metformin use. In this study, the users of sitagliptin or exenatide in the past 30 days had an increased risk of AP (OR 2.24 [95% CI 1.36–3.68], P = 0.01) relative to the odds of nonusers (3).

Type 2 diabetes is a condition that has been shown to have an increased incidence of AP (13), which is probably related to a high prevalence of risk factors for AP in these patients, such as chronic pancreatitis, alcohol abuse, severe hypertriglyceridemia, and gallstone disease (14). The inability to adjust for imbalance in the aforementioned risk factors was probably the reason for the controversial results of previous predominantly observational studies, including meta-analyses (2–6).

The main limitation of the current study is that it was not a traditional meta-analysis based on a complete search of the literature, which could have led to a selection bias. On the other hand, our focus on three large randomized trials has several strengths. First, as a result of the randomization, the background therapy of patients with drugs that might increase the risk for AP was most probably balanced between the drug and placebo groups. Therefore, the only pharmacological difference in the intervention was the treatment with a gliptin in the active intervention group and the higher rate of use of the other antidiabetic drugs in the placebo arm in comparison with the

gliptin arm. None of the drugs used for the treatment intensification in either arm were previously reported to decrease or increase the incidence of AP. Thus, we presume, in accordance with the observational study of Singh et al. (3), in which adjustment for several risk factors for AP was performed, that the signal for increased incidence of AP might have been related to the treatment with a gliptin. Second, a randomized design of all three studies also balanced the risk factors for AP in gliptin and placebo groups. Third, in contrast with the predominantly short-term randomized trials, the three trials included had a mean duration at least of 1.5 years with an exposure to the gliptins that was long enough to trigger AP in predisposed subjects. Each one of these studies, however, was powered to show the noninferiority of the gliptin-treated group compared with the control group with respect to the incidence of CV events, but it was not powered enough to show a difference in the incidence of AP (9–11). We think that the present analysis that pooled the data from three trials has sufficiently increased the statistical power to also detect the difference in the incidence of this rare event.

Although the treatment with gliptins compared with placebo resulted in a significant increase in the relative risk of AP incidence by 79% in patients with type 2 diabetes, the absolute increase in risk was only 0.13%, which is quite low because it means that for 1,000 gliptin-treated patients we may anticipate one to two extra cases of AP during a 2-year period.

We therefore conclude that gliptin treatment slightly, but significantly, increases the risk of AP in patients with type 2 diabetes.

Funding. This research was supported by research grants from the Ministry of Education, Slovakia (APVV-0134-11 and VEGA 1/0389/14).
Duality of Interest. I.T. has served on advisory boards for Boehringer Ingelheim, AstraZeneca, Eli Lilly and Company, Novo Nordisk, Takeda, Sanofi, and Servier and has served on speakers bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Johnson & Johnson, Sanofi, Servier, and Worwag Pharma. I.R. has served on advisory boards for AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Medscape, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Orgenesis, SmartZyme Innovation Ltd., and LabStyle Innovations Corp.; has served as a consultant for AstraZeneca/Bristol-Myers Squibb, Insuline Medical Ltd., Gili Medical, Kamada, and FuturRx Ltd.; has served on speakers' bureaus for AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Johnson & Johnson, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Teva; and is a stockholder/shareholder in Insuline Medical, LabStyle Innovations Corp., SmartZyme Innovation Ltd., Orgenesis, and Glucome Ltd.
Author Contributions. I.T. researched the literature and drafted and critically revised the article. I.R. researched the literature and critically revised the article. Both authors take responsibility for the contents of the article. I.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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