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Original Research

Efficacy and Cardiovascular Safety of Linagliptin as an Add-On to Insulin in Type 2 Diabetes: A Pooled Comprehensive Post Hoc Analysis

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ABSTRACT

Objective: With the expanding armamentarium of noninsulin therapies for type 2 diabetes mellitus, the use of insulin with various oral agents is becoming more common. In this study, we assessed the efficacy and cardiovascular (CV) safety of the dipeptidyl peptidase-4 inhibitor linagliptin as add-on to insulin in patients with type 2 diabetes.
Methods: In this post hoc analysis, data for patients receiving basal or basal-bolus insulin were pooled from 4 randomized, double-blind, phase 3 clinical trials of linagliptin 5 mg once daily or placebo given as add-on to background glucose-lowering treatment. Changes in glycated hemoglobin (A1C) and CV risk factors were assessed from baseline to end of trial. The primary CV endpoint was a composite of CV death, nonfatal myocardial infarction, nonfatal stroke and hospitalization due to unstable angina.
Results: The number of patients receiving basal or basal-bolus insulin as background therapy was 1613 (linagliptin: n=811; placebo: n=802). The placebo-adjusted mean (SE) change from baseline in A1C was –0.41 (0.05)% (95% CI –0.50, –0.32; p<0.0001). Treatment with linagliptin provided a relative weight benefit and reduced insulin requirements without affecting blood pressure, heart rate or lipids. The incidence of hypoglycemia with linagliptin was similar to that for placebo (38.7% vs. 39.4%, respectively). The hazard ratio (HR) for the primary endpoint showed that treatment with linagliptin was not associated with an increased CV risk (HR 1.07 [95% CI 0.62, 1.85]).
Conclusions: Linagliptin, when added to ongoing insulin treatment in patients with type 2 diabetes, improves glycemic control and has a neutral impact on major adverse CV events.

Mots clés :
risque cardiovasculaire
inhibiteur de la DPP-4
insuline
linagliptine
diabète sucré de type 2

RÉSUMÉ

Objectif : En raison de la croissance de l'arsenal thérapeutique composé de traitements non insuliniques contre le diabète sucré de type 2, la combinaison de l'insuline et de différents agents oraux est de plus en plus fréquente. Dans la présente étude, nous avions évalué l'efficacité et l'innocuité sur le plan cardiovasculaire (CV) de la linagliptine, un inhibiteur de la dipeptidyl peptidase-4, comme traitement d'appoint à l'insuline chez les patients souffrant du diabète de type 2.
Méthodes : Dans cette analyse *post-hoc*, nous avions regroupé les données sur les patients recevant l'insuline basale ou basale-bolus qui provenaient de 4 essais cliniques de phase III à répartition aléatoire, à double insu, sur la linagliptine à raison de 5 mg 1 fois par jour ou le placébo donné comme traitement d'appoint au traitement hypoglycémiant de fond. Nous avions évalué les changements de l'hémoglobine glyquée (A1c) et les facteurs de risque CV du début à la fin de l'essai. Le critère de jugement principal sur le plan CV était un critère composite regroupant la mortalité CV, l'infarctus du myocarde non fatal, l'accident vasculaire cérébral non fatal et l'hospitalisation en raison d'une angine instable.

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Résultats : Le nombre de patients recevant l'insuline basale ou basale-bolus comme traitement de fond était de 1613 (linagliptine : n=811; placébo : n=802). La variation moyenne (SE) de l'A1c par rapport au départ, ajustée selon le placébo, était de –0,41 (0,05) % (IC à 95 % –0,50, –0,32; p<0,0001). Le traitement par linagliptine a montré un avantage relatif sur le poids et a réduit les besoins en insuline sans nuire à la pression artérielle, à la fréquence cardiaque ou aux lipides. La linaligliptine montrait une incidence de l'hypoglycémie comparable au placébo (38,7 % *vs* 39,4 %, respectivement). Le rapport de risque (RR) du critère de jugement principal a montré que le traitement par linagliptine n'était pas associé à une augmentation du risque CV (RR 1,07 [IC à 95 % 0,62, 1,85]).
Conclusions : La linagliptine lorsque qu'elle est combinée au traitement à l'insuline en cours chez les patients souffrant du diabète de type 2 améliore la maîtrise glycémique et a un effet neutre sur les événements CV indésirables majeurs.

Introduction

The progressive nature of type 2 diabetes mellitus and the lack of treatment options that have sustainable effects on glucose control usually necessitate additions and changes in treatment during the course of the disease. Current treatment guidelines initially recommend metformin monotherapy as first-line therapy, unless patients present with marked hyperglycemia (high glycated hemoglobin [A1C] levels) (1–4). For patients who fail to reach or maintain therapeutic targets when taking metformin, there are a number of oral antihyperglycemic drugs (OADs) that can be added to the regimen for use as dual or triple therapy, including a sulfonylurea, a dipeptidyl peptidase (DPP)-4 inhibitor, a sodium-glucose cotransporter-2 inhibitor or a thiazolidinedione. Ultimately, many patients with type 2 diabetes will eventually require insulin therapy to maintain adequate glycemic control, either insulin alone or in combination with their existing OADs (1).

Because of the expanding armamentarium of noninsulin therapies for type 2 diabetes, there has been a shift toward initiating insulin later rather than early in the course of this progressive disease (5). Consequently, patients with type 2 diabetes have relatively advanced disease states at the time of insulin initiation, including vascular dysfunctions and higher cardiovascular (CV) risks (6). Observational studies have shown CV risk factors and CV incidence rates to be higher in patients with type 2 diabetes who are treated with insulin relative to patients not treated with insulin, as reported by Currie et al, who examined the risk for adverse events (AEs) (including CV events) associated with glucose-lowering therapies in patients with type 2 diabetes (7). In their study, using observational registry data from the United Kingdom General Practice Research Database 2000-2010, a notably higher event rate of nonfatal myocardial infarction (MI), nonfatal stroke or CV death (3-point [3P] major adverse cardiac event [MACE]) (16.7 events per 1000 person-years) and all-cause mortality rate (46.0 events per 1000 person-years) was observed in patients receiving insulin monotherapy compared with all other regimens (metformin monotherapy, metformin plus insulin, metformin plus sulfonylurea) apart from sulfonylurea, and also showed increased adjusted hazard ratios (HRs) for these parameters (1.736 and 2.197, respectively). Other observational studies have reported increased CV risks in insulin-treated patients with type 2 diabetes, showing a >2.5-fold increased risk for CV events with insulin use, either alone or in combination with other OADs (8), and an increased risk for MI, compared with other OADs (9).

Concerns about hypoglycemia often prevent patients and their physicians from uptitrating basal insulin when glucose levels are above the target level. Combining insulin with a DPP-4 inhibitor is a valuable option for improving glycemic control in the setting of insulin-treated patients with type 2 diabetes, as shown in previous clinical trials (10–15). It is interesting that apart from having an impact on the pancreatic beta cells, mechanistic studies have suggested that DPP-4 inhibition may improve pancreatic alpha-cell function (16–18). Linagliptin is a DPP-4 inhibitor that, in previous phase 3 trials that included elderly patients and patients with renal impairment, was shown to improve glycemic control with a favourable safety and tolerability profile (19–22). It is important to note that linagliptin does not appear to increase the risk for hypoglycemia or weight gain. In addition, consistent with other DPP-4 inhibitors, no increased CV risk has been observed in a meta-analysis of linagliptin studies (23). In a phase 3 study, linagliptin added to basal insulin therapy in patients with inadequate glycemic control significantly reduced A1C levels by –0.6% and was well tolerated, without increased risks for hypoglycemia or weight gain, compared with placebo (24).

To evaluate the efficacy and CV safety of linagliptin as an add-on to insulin in a patient population at increased risk for CV events, we undertook a post hoc pooled analysis of data from all patients with type 2 diabetes who were receiving treatment with basal or basal-bolus insulin therapy (24–27).

Methods

Study selection and populations

For this post hoc analysis, efficacy and CV safety data for patients receiving basal or basal-bolus insulin were pooled from 4 randomized, double-blind, phase 3 clinical trials in the linagliptin clinical trials program (24–27), in which all CV events were adjudicated by an independent clinical event committee (CEC). Patients with type 2 diabetes were treated with linagliptin 5 mg once daily or placebo as monotherapy or as add-on therapy to various background glucose-lowering drugs (Table 1). These trials ranged from 12 to ≥52 weeks; in 1 trial (24), patients who had been randomized early in the study were treated for longer than 52 weeks until the study closeout, which occurred as soon as all patients had been treated for at least 52 weeks. A 12-week trial also included a 40-week active-controlled extension period during which patients originally randomized to placebo were switched to glimepiride (26).

All protocols were approved by the independent ethics committees or institutional review boards of all participating centres. The studies were carried out according to the principles of the Declaration of Helsinki and the International Guideline for Good Clinical Practice. All patients provided written informed consent prior to participation in the studies.

Common inclusion criteria across the trials included diagnoses of inadequately controlled type 2 diabetes (A1C ≥7.0% to ≤10.0%). Of the trials, 3 enrolled patients who were 18 years of age or older and had body mass indices ≤45 kg/m^2 (24,26,27). In 1 trial, eligible patients were 70 years of age or older (25). Patients underwent a 2-week, open-label, placebo run-in period and were then randomized to receive double-blind treatment with either linagliptin or placebo once daily. Further details about the design and methodology of these trials are found in the individual publications (24–27).