Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Efficacy and safety of the addition of a dipeptidyl peptidase-4 inhibitor to insulin therapy in patients with type 2 diabetes: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 8 March 2015
Received in revised form
2 March 2016
Accepted 11 March 2016
Available online 23 April 2016

Keywords:
Dipeptidyl peptidase-4 inhibitor
Insulin
Meta-analysis
Systematic review
Type 2 diabetes

ABSTRACT

Aims: To compare the efficacy and safety of the addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor or a placebo in patients with type 2 diabetes inadequately controlled with insulin.
Methods: We searched randomised controlled trials (RCTs) from MEDLINE, EMBASE, LILACS, the Cochrane Central Register of Controlled Trials and the ClinicalTrials.gov online registry. Studies of at least 12 week treatment duration were eligible if they were RCTs in patients with type 2 diabetes comparing addition of a DPP-4 inhibitor to insulin therapy (INS/DPP4i) with addition of a placebo to insulin therapy (INS/PCB) and contained information on the change in glycated haemoglobin (HbA1c) from baseline.
Results: Of 3105 potentially relevant published articles and 206 registered trials, 9 studies were included for meta-analysis. Compared to INS/PCB, INS/DPP4i exhibited a greater reduction in HbA1c (weighted mean difference [WMD] −0.58%; 95% CI −0.70, −0.46) and fasting plasma glucose (WMD −0.59 mmol/L; 95% CI −0.79, −0.40) with less daily insulin doses (WMD −1.86 IU; 95% CI −3.27, −0.45) and with no difference in weight gain (WMD −0.04 kg; 95% CI −0.25, 0.16). The risk of hypoglycaemia was similar between INS/DPP-4i and INS/PCB (the RR in favour of INS/PCB was 0.94; 95% CI 0.84, 1.05).
Conclusions: Compared to placebo, DPP-4 inhibitors exhibit a better glycaemic control without further increasing the risk of weight gain and hypoglycaemia in patients with type 2 diabetes inadequately controlled with insulin.

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http://dx.doi.org/10.1016/j.diabres.2016.03.011
0168-8227/

1. Introduction

The prevalence of diabetes is reaching pandemic proportions, with 382 million people worldwide currently estimated as having the disease [1]. Type 2 diabetes is regarded as the result of complex pathogenic mechanisms including pancreatic beta-cell dysfunction, peripheral insulin resistance, increased hepatic glucose production, non-suppressed postprandial glucagon secretion, decreased incretin effect, and many others [2]. Pancreatic beta-cell dysfunction, in particular, is the prerequisite of type 2 diabetes and relentlessly progresses over time [3]. Therefore, many patients with type 2 diabetes exhibit progressive worsening of glycaemic control and do not respond adequately to oral medications, which eventually necessitates the initiation of insulin therapy [4]. Unlike oral antidiabetic medications, insulin therapy has virtually no limit in terms of the glucose-lowering effect. However, insulin therapy possesses two major drawbacks: weight gain and hypoglycaemia [5]. The most common practice in the initiation of insulin therapy in patients with type 2 diabetes is to use a basal insulin on top of pre-existing oral antidiabetic medications [6]. If basal insulin alone is not adequate for good glycaemic control, a pre-meal bolus of insulin can be added or changed to premixed insulins [5]. However, intensification of the insulin regimen is commonly associated with an increased risk of hypoglycaemia and/or increased body weight [7]. Therefore, a better strategy is needed to minimise the risk of adverse effects accompanied by an intensified insulin therapy.

Adding incretin-based therapy (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists or dipeptidyl peptidase-4 [DPP-4] inhibitors) to pre-existing insulin therapy has been suggested as an alternative option instead of intensifying insulin regimens [8]. Incretin hormones such as glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are secreted from gastrointestinal endocrine cells in response to oral nutrient ingestion and augment glucose-stimulated insulin secretion from pancreatic beta-cells [9–11]. Among incretin hormones, GLP-1 has been developed as an anti-diabetic agent because GLP-1, and not GIP, maintains its insulinotropic effect in patients with type 2 diabetes [12]. Furthermore, GLP-1 decreases postprandial glucagon secretion in patients with type 2 diabetes [9–11]. Interestingly, GLP-1 stimulates insulin secretion and suppresses glucagon secretion only in a hyperglycaemic condition [13]. This glucose-dependent mechanism of action of GLP-1 is accompanied by a decreased risk of hypoglycaemia [11,14]. In addition, GLP-1 reduces body weight by decreasing appetite and increasing satiety [9–11]. In accordance with these observations, a recent meta-analysis revealed that GLP-1 receptor agonists combined with basal insulin therapy decreased HbA1c and reduced body weight without increasing the risk of hypoglycaemia compared to other anti-diabetic treatments [15], which could be ascribed to the complementary nature of GLP-1 and insulin on glycaemic control [8].

DPP-4 inhibitors increase active GLP-1 and GIP levels in plasma that can stimulate insulin secretion and suppress glucagon secretion [11,16]. However, there are many endogenous peptides other than GIP and GLP-1 that can be degraded by the enzymatic action of DPP-4 [17]. As such, DPP-4 inhibitors may exhibit different effects compared to GLP-1 receptor agonists. Unlike GLP-1 receptor agonists, DPP-4 inhibitors do not decelerate gastric emptying or reduce body weight [11,16]. DPP-4 inhibitors are orally taken and do not increase the incidence of nausea and vomiting [11,16]. Nonetheless, the mechanism of the glucose-lowering effect of DPP-4 inhibitors is also complimentary to insulin [8]. In this regard, we set out a systematic review and meta-analysis on the effect of DPP-4 inhibitors added to insulin therapy in patients with type 2 diabetes.

2. Materials and methods

We conducted a systematic review and meta-analysis according to the pre-developed protocol by the authors that specified the eligibility, data sources, searching strategy, outcome variables, data selection methods and main analyses and described the results following the PRISMA (preferred reporting items for systematic review and meta-analyses) recommendations [18].

2.1. *Eligibility criteria*

Randomised controlled trials (RCTs) were considered eligible when they compared the addition of a DPP-4 inhibitor to insulin therapy (INS/DPP4i) with the addition of a placebo to insulin therapy (INS/PCB), were based on at least 12 weeks of treatment duration, were performed in type 2 diabetes mellitus patients, were described in English and contained information on the change in glycated haemoglobin (HbA1c) from baseline. Studies were excluded when they did not have any available information on the change in HbA1c values in the form of the mean and the standard error or its equivalents such as 95% CI and standard deviation, which can be used for calculation of standard error of the placebo-subtracted change in HbA1c value between INS/DPP4i and INS/PCB in a given study. Any duplicate or extension of one study was excluded.

2.2. *Data sources and search strategies*

We performed searches of electronic databases for published articles on MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL). We also retrieved clinical trials with results not yet published on ClinicalTrials.gov. The search terms included the keywords “DPP-4 inhibitor”, “vildagliptin”, “sitagliptin”, “linagliptin”, “alogliptin”, “saxagliptin”, “gemigliptin”, “dutogliptin”, “gosogliptin”, and “insulin” combined with the substance names of DPP-4 inhibitors. The elaborated search strategy per each database is described in Appendix A. The last search was conducted on October 4, 2014.

2.3. *Study selection*

Two reviewers (SHM and YGK) independently collected and selected the studies as follows. Collected publications from