Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

The efficacy and safety of DPP4 inhibitors in patients with type 1 diabetes: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 24 March 2016
Received in revised form
10 August 2016
Accepted 19 August 2016
Available online 28 September 2016

Keywords:
Type 1 diabetes
DPP4 inhibitors
Meta-analysis

ABSTRACT

Aims: Dipeptidyl peptidase-4 (DPP4) inhibitors are a novel class of antidiabetic medication in the treatment of type 2 diabetes mellitus. Several studies have indicated that DPP4 inhibitors could be used for type 1diabetes (T1DM). Here, we performed a meta-analysis to assess the efficacy and safety of DPP4 inhibitor therapy in patients with T1DM.

Methods: We conducted searches on Medline, Cochrane Library, Web of Science, and EMBASE for relevant studies published before November 21, 2015. Mean difference (MD) with 95% confidence interval (CI) was calculated for the mean glycated hemoglobin (HbA1c) changes and insulin dosage from baseline to endpoint. Risk ratio (RR) with 95% CI was calculated for severe hypoglycemia. Data was extracted by two independent reviewers, and the meta-analysis was performed using Review Manager version 5.3.

Results: Six randomized controlled trials with a total of 228 individuals were finally included into the meta-analysis. DPP4 inhibitors reduced daily insulin dosage significantly (MD −2.41 U/day, 95% CI [−3.87, −0.94], $P = 0.001$) but did not reduce HbA1c level (MD 0.0% (0 mmol/mol), 95% CI [−0.16, 0.15], $P = 0.97$). Furthermore, DPP4 inhibitors did not change the incidence of severe hypoglycemia (RR 0.81, 95% CI [0.34, 1.93], $P = 0.64$).

Conclusion: In patients with T1DM, DPP4 inhibitors combined with insulin do not increase or decrease the risk of hypoglycemia and do not decrease HbA1c levels.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune-mediated disease resulting from the selective and progressive destruction of insulin-producing beta-cells in pancreatic islets [1]. The most recent guidelines and algorithms recommend insulin therapy as the main mode of glucose control in T1DM mellitus. Intensive glucose control is associated with a significant

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http://dx.doi.org/10.1016/j.diabres.2016.08.022
0168-8227/

reduction in both micro- and macrovascular complications in T1DM patients. Many patients still cannot reach the recommended goal in glycated hemoglobin (HbA1c) levels despite being treated with intensive insulin injections. However, increasing the dosage of insulin is always associated with weight gain and increases the risk of hypoglycemia.

Dipeptidyl peptidase-4 (DPP4) inhibitors are a novel type of oral glucose-lowering agent that modulate fasting plasma glucose, postprandial glucose, and HbA1c levels by decreasing the inactivation of endogenous incretins to stimulate the release of insulin in a glucose-dependent manner [2–4]. This class of drugs includes sitagliptin, vildagliptin, linagliptin, saxagliptin, alogliptin, and dutogliptin. Combining insulin with a DPP4 inhibitor has been well documented to reduce HbA1c levels with less weight gain and incidence of hypoglycemia in patients with type 2 diabetes (T2DM) [5].

A recent study showed that there was a significant reduction in HbA1c with sitagliptin compared with placebo in patients with T1DM [6], while other randomized control trials did not find significant differences in HbA1c levels between patients with DPP4 inhibitors and placebo [7]. A meta-analysis is a good way to summarize the available data to provide more robust results than the individual study. The aim of this study was to perform a systematic review and meta-analysis of the safety and efficacy of DPP4 inhibitors for the treatment of T1DM.

2. Materials and methods

2.1. Identification and eligibility of relevant studies

According to the Preferred Reporting Items for Systematic Reviews And Meta-Analysis guidelines [8], all the studies we captured were published before November 21, 2015 in PubMed, EMBASE, Web of science, and the Cochrane Library based on the following search terms: (1) “sitagliptin”, “vildagliptin”, “saxagliptin”, “alogliptin”, “linagliptin”, “dipeptidyl peptidase-4 inhibitors” combined and (2) “type 1 diabetes”, “LADA”, “autoimmune diabetes”. Ongoing and unpublished studies were identified by searching the web site of the Chinese State Food and Drug Administration, clinicaltrialsregister.eu and clinicaltrials.gov. No restriction was imposed on search language. The studies included in this meta-analysis met the following criteria: (1) they were randomized controlled trials, (2) they used a parallel design or crossover design of DPP4 inhibitors and insulin versus placebo treatment (or single insulin therapy), and (3) they reported data on HbA1c change (from baseline to endpoint), insulin dosage, and hypoglycemia. Case-only studies, case reports, or reviews were all excluded. Identification of relevant abstracts and the selection of studies were performed by two independent investigators. The conflicts were solved through discussion and consensus with a third investigator.

2.2. Data extraction

The following information was sought from each trial: authors, ethnicity, study design, sample sizes, DPP4 therapy, duration of treatment, type of patient, mean age, and duration of diabetes. Relevant information is shown in detail in Table 1.

2.3. Statistical analysis

The effect sizes and pooled estimates of the effects across the trials were calculated and analyzed with Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) from the Cochrane Collaboration. The mean difference between two groups of the studies was measured as effect size. Risk ratio (RR) of the dichotomous outcomes was used to evaluate the risk of hypoglycemia for each trial.

The heterogeneity was assessed using the Cochran Q statistic (significance level at $P < 0.10$) and the I^2 statistic which was also quantitative analysis of heterogeneity (I^2 = 0–25%: low heterogeneity; I^2 = 25–50%: moderate heterogeneity; I^2 = 50–75%: substantial heterogeneity; I^2 = 75–100%: extreme heterogeneity) [9].

Finally, we evaluated the risk of bias using the Cochrane Collaboration’s “risk of bias” tool [10] to summarize the risk of bias across studies for selection bias, performance bias, attrition bias, and reporting bias. The quality of evidence for each outcome was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [11], and GRADE profiler was used to create a GRADE evidence profile (version 3.6.1, GRADE Working Group). Publication bias was assessed using a funnel plot [12], a scatter plot of studies’ mean difference against standard errors. The plot resembles a symmetrical inverted funnel in the absence of bias, and is skewed if there is a bias. A sensitivity analysis was also conducted by sequentially excluding one study each time to see whether the findings were robust.

3. Results

3.1. Literature selection

We initially retrieved 227 relevant publications from PubMed, the Cochrane Library, Web of Science, and EMBASE. The majority of the articles were excluded after screening the titles or abstracts, mainly because there were duplications, irrelevant studies, or they were not randomized trials. Seven articles had performed detailed assessment and two of them did not provide the data we required. For one study, we got the data we needed from the corresponding author [6]. The other studies which did not provide endpoint data for HbA1c or changes of HbA1c from baseline were excluded [13]. Finally, six randomized controlled trials were retained for the following meta-analysis [6,7,14–17]. Three of them were crossover design studies, and for which, data from the first period was extracted and used in the meta-analysis. A flow chart showing the study selection is presented in Fig. 1.

3.2. Study characteristics

The characteristics of the six enrolled studies are shown in Table 1. Four double-blinded randomized controlled trials were conducted in Caucasians and two open label random-