Diabetes & Metabolism xxx (2017) xxx–xxx

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Review

Dipeptidyl peptidase-4 inhibitors and risk of arthralgia: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 27 April 2017
Accepted 23 May 2017
Available online xxx

Keywords:
Arthralgia
Dipeptidyl peptidase-4 inhibitors
Meta-analysis
Systematic review

ABSTRACT

Background. – The US Food and Drug Administration has warned that treatment with dipeptidyl peptidase (DPP)-4 inhibitors may promote serious arthralgia. However, the clinical evidence for this is relatively lacking.
Objective. – For this reason, a systematic review and meta-analysis of randomized controlled trials (RCTs) were carried out to determine the relationship between DPP-4 inhibitors and risk of arthralgia, and also to investigate any potential risk factors.
Methods. – An extensive electronic search for RCTs comparing DPP-4 inhibitors with any comparators was performed up to July 2016. Outcomes of interest were overall and serious arthralgia. Summary risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.
Results. – A total of 67 RCTs (involving 79,110 patients) was ultimately included. Pooled results showed that DPP-4 inhibitors were associated with a slightly but significantly increased risk of overall arthralgia (RR: 1.13, 95% CI: 1.04–1.22; $P = 0.003$) and a non-significant increased risk of serious arthralgia (RR: 1.44, 95% CI: 0.83–2.51; $P = 0.20$). Also, subgroup analyses showed that add-on/combination therapy and longer diabetes duration (> 5 years) were possible factors associated with the increased risk of overall arthralgia.
Conclusion. – These findings suggest that DPP-4 inhibitors can increase the risk of arthralgia. Thus, the benefits of glycaemic control must be weighed against the risk of arthralgia when prescribing DPP-4 inhibitors. Further studies are now needed to identify and confirm these risk factors.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease with multiple complications that constitute an enormous cost and public-health burden worldwide, and its prevalence and incidence is rapidly increasing. Indeed, it is estimated by the International Diabetes Federation (IDF) that there were 415 million people with diabetes in 2015 and that, by 2040, that number will have risen to 642 million all over the globe [1].

Dipeptidyl peptidase (DPP)-4 inhibitors are a class of incretin-based agents for treating T2DM. They act by increasing postprandial concentrations of glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP) [2–4]. GLP-1 and GIP stimulate insulin secretion in a glucose-dependent manner, suppressing glucagon secretion and slowing gastric emptying. DPP-4 inhibitors have become one of the emerging treatment options available for patients who fail to achieve glycaemic control with metformin alone or in combination with lifestyle management, or when metformin is not an option according to the major international diabetes guidelines [5]. The non-incretin effects of DPP-4 inhibitors have also been investigated, such as their influence on immune and inflammatory function [6,7].

Arthralgia is a non-specific symptom that may be chemically induced or related to underlying autoimmune disorders [8]. In

Abbreviations: DPP-4, Dipeptidyl peptidase-4; FDA, Food and Drug Administration; GIP, Glucose-dependent insulinotropic peptide; GLP-1, Glucagon-like peptide-1; IDF, International Diabetes Federation; MedDRA, Medical Dictionary for Regulatory Activities; RA, Rheumatoid arthritis; RCTs, Randomized controlled trials.

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http://dx.doi.org/10.1016/j.diabet.2017.05.013
1262-3636/

August 2015, the US Food and Drug Administration (FDA) warned that DPP-4 inhibitors can cause serious arthralgia, raising safety issues concerning the entire drug class, and encouraging healthcare professionals and patients to pay close attention [9]. A search of the FDA Adverse Event Reporting System (FAERS) database identified 33 cases of serious arthralgia reported with the use of DPP-4 inhibitors between October 2006 and December 2013. So far, some reviews [10–14] have revealed that such adverse events may be more frequent in DPP-4 inhibitor-exposed groups. These findings raise grave concerns among health professionals and healthcare authorities.

To provide an up-to-date and comprehensive picture of the association between DPP-4 inhibitors and risk of arthralgia, a systematic review and meta-analysis was performed to assess the extent to which DPP-4 inhibitors affect the risk of arthralgia in patients with T2DM, and also to determine the potential risk factors.

Materials and methods

Our systematic review met predetermined methodological criteria, and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15] for reporting on our findings.

Data sources and searches

A comprehensive literature search was performed of PubMed, Embase and Cochrane Central Register of Controlled Trials up to 6 July 2016. The search terms were 'dipeptidyl peptidase-4 inhibitors', 'sitagliptin', 'vildagliptin', 'saxagliptin', 'linagliptin' and 'alogliptin'. Reference lists in the retrieved articles and supplemental materials were also examined manually to further identify any potentially relevant studies. In addition, the ClinicalTrials.gov website was searched, using the generic names of each drug to identify any other eligible clinical trials. The search was limited to studies labelled 'completed' or 'terminated' for which summary results were available. Furthermore, the drug manufacturers' websites were searched for any additional information.

Study selection

Randomized controlled trials (RCTs) were eligible if they fulfilled the following inclusion criteria:

- conducted in patients with T2DM;
- conducted with any comparison of DPP-4 inhibitors and placebo, lifestyle modification or active antidiabetic drugs;
- explicitly reported numbers of arthralgia events in all treatment groups as either raw data or adjusted effect estimates with 95% confidence intervals (CIs).

Trials with zero arthralgia events were not included. Arthralgia was defined as an unspecified clinical outcome as per the Medical Dictionary for Regulatory Activities (MedDRA; preferred term level: 10003239). No age, language or date restrictions were applied.

Two reviewers independently screened all titles, abstracts and full texts for eligibility. Studies were retrieved for further consideration if adjudged pertinent by at least one reviewer. The reviewers dealt with discrepancies through discussion and, if necessary, a third reviewer was consulted. When there were multiple reports of the same trial, the most complete and/or most recently reported data were chosen.

Data extraction and quality assessment

The following information was extracted from each eligible RCT:

- study characteristics (author(s) name(s), year of publication, trial registry number, number of countries involved, number of study sites, total number of patients randomized, duration of follow-up); patients' characteristics [gender, age, duration of diabetes, body mass index (BMI) and baseline HbA_{1c} level];
- interventions [baseline treatment, generic name of DPP-4 inhibitor(s) and control group(s)];
- outcomes (number of events and of patients included for analyses in each group).

Two types of adverse event data were usually reported on clinicaltrials.gov: 'serious'; and 'other' (frequency $> 5\%$ excluding serious events). Arthralgia events reported within these two types were extracted, with those listed in the 'Serious Adverse Events' section of the ClinicalTrials.gov website identified as 'serious' arthralgia, while both types of adverse events were combined as 'overall' arthralgia events.

For extension studies, if the treatment assignment was switched from placebo to DPP-4 inhibitors, only the outcome data up to that point were documented; if the treatment assignment was switched from placebo to active drugs other than DPP-4 inhibitors, the outcome data from the longer follow-up time were documented. For studies with multiple arms, all DPP-4 inhibitor arms were combined into a DPP-4 inhibitor group, while comparators constituted an overall control group. For studies reporting outcomes at various time points, the results from the longest observational periods were used.

Two reviewers also independently assessed the quality of the included studies. Discrepancies were resolved by discussion or through consultation with a third reviewer. The potential risk of bias in these RCTs was assessed according to criteria developed with the Cochrane risk-of-bias tool [16].

Statistical analysis

The risk of overall arthralgia and serious arthralgia with DPP-4 inhibitors was evaluated by calculating risk ratios (RRs) and 95% CIs. $P < 0.05$ was considered statistically significant. Meta-analyses were performed using STATA (version 12) software (StataCorp., College Station, TX, USA). Heterogeneity was assessed by Cochrane χ^2 test and I^2 statistic. A significant Q-statistic test result ($P < 0.05$) indicated a substantial level of heterogeneity [17]. The I^2 statistic describes the percentage of variability in effect estimates as the result of heterogeneity rather than as a sampling error (chance), with I^2 values $\geq 50\%$ indicating a substantial level of heterogeneity. If the I^2 is $< 50\%$, a fixed effects model was then called for. Pooled results were displayed by forest plots.

To explore any potential risk factors that might affect the probable association between risk of arthralgia and DPP-4 inhibitors, four prespecified subgroup analyses were conducted, according to mode of treatment (monotherapy or combination therapy), type of control (placebo or active comparator), duration of follow-up (≤ 26 weeks or > 26 weeks) and mean duration of diabetes (≤ 5 years or > 5 years). Any potential publication bias was assessed by Egger's test.

In addition, sensitivity analyses were carried out using alternative effect measures [odds ratios (ORs) *vs* RRs], alternative pooling methods (Peto *vs* Mantel–Haenszel) and statistical models of heterogeneity (random *vs* fixed effects). Such analyses were also conducted to investigate the influence of each separate study on the pooled results by omitting one study at a time, using STATA's user-written 'metaninf' function.

Please cite this article in press as: Men P, et al. Dipeptidyl peptidase-4 inhibitors and risk of arthralgia: A systematic review and meta-analysis. Diabetes Metab (2017), http://dx.doi.org/10.1016/j.diabet.2017.05.013