Saudi Pharmaceutical Journal (2015) **23**, 603–613

King Saud University

Saudi Pharmaceutical Journal

www.ksu.edu.sa
www.sciencedirect.com

REVIEW

Systematic review and meta-analysis of efficacy and safety of combinational therapy with metformin and dipeptidyl peptidase-4 inhibitors

Abdulrahman S. Alanazi *

Department of Clinical Pharmacy, Unaizah College of Pharmacy, Qassim University, P.O. Box 1627, Hail 81441, Saudi Arabia

Received 24 October 2013; accepted 14 December 2013
Available online 3 January 2014

KEYWORDS

Metformin;
Dipeptidyl peptidase-4 inhibitors;
DPPIs;
Diabetes mellitus;
Combinational therapy

Abstract Combinational therapies are often required in the management of type 2 diabetes mellitus (T2DM). Among the important candidates, dipeptidyl peptidase-4 inhibitors (DPPIs) and metformin combination (DPPI-MET) have shown promising endeavors. In order to examine the efficacy and safety of such a combination therapy in T2DM patients finding inadequate control with metformin, this systematic review and meta-analysis has been conducted. Literature search was made in multiple electronic databases. Inclusion criteria included; RCTs examining the efficacy and safety of DPPI-MET against placebo-MET or MET-only groups of T2DM patients by observing changes in disease endpoints including HbA1c and FPG, and the length of trial be at least 12 weeks. Mean differences based meta-analyses were performed and heterogeneity assessment was carried out. Nineteen studies were selected and included in the meta-analyses. DPPI-MET significantly improved all disease endpoints and the difference could be noticed up to 2 years in the majority of outcome measures. In comparison with PBO-MET, the DPPI-MET combinational therapy resulted in the percent HbA1c changes from baseline with a mean difference [95% CI] of −0.77 [−0.86, −0.69] in 3-month ($P < 0.00001$), −0.67 [−0.76, −0.59] in 6-month ($P < 0.00001$), −0.67 [−0.88, −0.47] in 1-year ($P < 0.00001$) and −0.36 [−0.53, −0.20] in 2-year trials ($P < 0.0003$). Reduction in body weight and safety profile in the treated and control groups were not different. A combinational therapy with DPPI and metformin significantly improves diabetes clinical indicators and this effect has been observed for up to 2 years herein. Safety and tolerability of DPPI-MET combination have been found well-manageable with a very similar adverse event profile in both treated and control groups.

* Mobile: +966 501744888.
E-mail address: Alanazi_abdulrahman@yahoo.com

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

1319-0164
http://dx.doi.org/10.1016/j.jsps.2013.12.018

Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) prevalence is increasing and this disease could be the seventh leading cause of mortality by 2030. At present, 350 million people are suffering from this devastating disease (WHO, 2013). Microvascular complications associated with diabetes lead to blindness, renal failure and organ loss besides stroke and heart disease related mortality is 2–4 times more in diabetes patients (Green and Feinglos, 2008). It is a progressive disease which often requires multimedication strategy in order to achieve better glycemic control. Lifestyle changes are the prime interventions after the diagnosis of diabetes but metformin is the first line drug to control the disease which may be followed by other drugs such as sulfonylurea, thiazolidinediones and insulin when metformin is found inadequate to control diabetes.

Amongst the add-on treatments, sulfonylurea and thiazolidinediones were studied but because of the higher prevalence of hypoglycemic events and other complications are considered as low priority options. More recent developments in this field include utilization of glucagon like peptide analogues, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPPIs) and sodium-glucose co-transporter-4 inhibitors (SGLTIs) which have potentials to be used as add-on treatments (Ahren, 2008; Nauck et al., 2009a,b; Kurosaki and Ogasawara, 2013).

Whereas, agonists of the glucagon-like peptide-1 (GLP-1) receptor provide pharmacological levels of GLP-1 activity, DPPIs increase concentrations of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the breakdown of these incretins (Drucker and Nauck, 2006; Kendall et al., 2009). Both these incretins improve glucose-dependent insulin release. Meal induced glucagon secretion is also believed to be suppressed by the GLP-1 (Deacon et al., 2004). A number of DPPI drugs have shown efficacy and tolerability potentials and in a meta-analysis of 62 studies, DPPIs as monotherapy were found to decline percent HbA_{1c} by −0.76% when compared to respective placebo or comparator groups (Park et al., 2012).

There is no study so far to meta-analyze the efficacy and safety of the DPPI-metformin combinational therapy against placebo-metformin or metformin only controls. This is important to evaluate this potential combinational therapy as many fixed-dose combinations of metformin and DPPI drugs are proposed and many are in different stages of development. This systematic review and meta-analysis therefore attempts to evaluate the efficacy and safety of the combinational therapy with metformin and DPPIs by examining the data generated from the randomized controlled trials (RCTs) that examined the effectiveness of this combination against placebo-metformin controls in T2DM patients finding metformin therapy inadequate.

2. Methods

2.1. Literature search

Multiple electronic databases were searched for the identification, selection and retrieval of the required research papers. These included Medline/Pubmed, EMBASE, SCOPUS, CINAHL, Google Scholar, Science Citation Index Expanded, Conference Proceedings Citation Index-Science, Cochrane Central Register of Controlled Trials and the ClinicalTrials.gov. Search engines were used with various combinations and phrases of the major MeSH terms including dipeptidyl peptidase-4 inhibitors, sitagliptin, alogliptin, saxagliptin, vildagliptin, linagliptin, dutogliptin, add-on treatment to metformin, combinational therapy, randomized controlled trial, efficacy, safety, tolerability, and diabetes. Lists of references of important articles were also screened for achieving comprehension in the literature search.

2.2. Inclusion and exclusion criteria

This meta-analysis and associated systematic review includes RCTs that examined the efficacy, safety and tolerability of DPPIs in combination with metformin during the years 2000 to September 2013. The participants of these trials were T2DM patients with inadequate control of disease with lifestyle changes and metformin therapy. Primary outcome measures of interest were percent glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), postpandrial glucose (PPG) levels, homeostatic model of assessment (HOMA)-IR (insulin resistance) and -beta (beta cell), proinsulin–insulin ratio (PI), and body weight changes. The inclusion criteria were: (a) RCTs that examined the efficacy and safety of DPPI-MET against PBO-MET or MET-only groups of T2DM patients, (b) the trials had examined the effects of intervention on at least HbA_{1c} and FPG as clinical indicators of disease condition, (c) Disease diagnosis in the participants achieved at least 1 year before the start of the trial and (d) Length of the trial be at least 12 weeks. Exclusion criteria were: (a) RCTs which compared DPPI with metformin as monotherapies, (b) RCTs that studied DPPI-MET against PBO-MET plus other antidiabetic drug/s, (c) RCTs that utilized other contemporary drugs