Vascular Pharmacology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Vascular Pharmacology

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

Review

Impact of dipeptidyl-peptidase 4 inhibitors on cardiovascular diseases

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ARTICLE INFO

Keywords:
Cardiovascular diesease
Dipeptidyl peptidase 4 inhibitor
Atherosclerosis
Heart failure
Myocardial infarction

ABSTRACT

Dipeptidyl peptidase 4 (DPP-4) inhibitor is a novel group of medicine employed in type 2 diabetes mellitus (T2DM),which improves meal stimulated insulin secretion by protecting glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) from enzymatic degradation. Cardiovascular diseases are serious complications and leading causes of mortality among individuals with diabetes mellitus. Glycemic control per se seems to fail in preventing the progression of diabetic cardiovascular complications. DPP-4 has the capability to inactivate not only incretins, but also a series of cytokines, chemokines, and neuropeptides involved in inflammation, immunity, and vascular function. Pre-clinical studies suggested that DPP-4 inhibitors may have potential cardiovascular protective effects in addition to their antidiabetic actions. In recent years, a number of clinical trials have been conducted to evaluate the effect of different DPP-4 inhibitors on the cardiovascular system. We herein review the available clinical studies in cardiovascular effects played by each DPP-4 inhibitor and discuss the prospective application of DPP-4 inhibitors on cardiovascular diseases.

1. Introduction

Dipeptidyl peptidase 4 (DPP-4) inhibitor is a novel group of medicine used in type 2 diabetes mellitus (T2DM). It provides protection for the incretin hormone GLP-1 and GIP from enzymatic degradation by DPP-4 to improve meal-stimulated insulin secretion by pancreatic beta cells [1]. In addition to their effective reduction in blood glucose levels, without inducing weight gain, DPP-4 inhibitors show favorable pharmacokinetics features and provide good efficacy and safety for the management of T2DM in clinical practice [2]. Currently approved DPP-4inhibitors are given in Table 1.

The prevalence of diabetes mellitus has increased significantly over the past years. Currently, there are 415 million people with diabetes worldwide. And the number of patients will rise up to 642 million in 2040 [3]. Cardiovascular diseases are serious complications and the leading causes of mortality among individuals with diabetes mellitus [4]. Evidences showed intensive glycemic control had a primary prevention effect in the early intervention, but no benefit and could be potentially harmful in the late course of the disease [5]. To prevent the progression of diabetic vascular complications and reduce cardiovascular events in patients with diabetes mellitus. More treatments should be taken into consideration beyond the glycemic control.

DPP-4 is a widely expressed glycoprotein that exists either as a transmembranous protein or in a soluble form in plasma [6]. It has the ability to inactivate not only incretins, but also a number of cytokines, chemokines, and neuropeptides involved in inflammation, immunity, and vascular function [7]. Pre-clinical and clinical studies reported that DPP-4 inhibitors may have potential cardiovascular protective effects in T2DM in addition to their antidiabetic actions [8]. We herein review the available clinical data on cardiovascular effects exhibited by each DPP-4 inhibitor and discuss the prospective use of DPP-4 inhibitors on cardiovascular diseases.

Abbreviations: AMI, acute myocardial infarction; BNP, Brain natriuretic peptide; CD26, cluster of differentiation 26; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CXCR4, chemokine receptor type 4; DPP-4, Dipeptidyl peptidase 4; DR, Diabetic retinopathy; EF, Ejection fraction; EPCs, endothelial progenitor cells; FDA, Food and Drug Administration; FMD, flow-mediated dilation; NO, Nitric oxide; GIP, glucosedependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HDL-C, High-density lipoprotein cholesterol; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IDL, intermediate density lipoprotein; IMT, The carotid intima-media thickness; IL, interleukin; LDL C, Low density lipoprotein cholesterol; LV, Left ventricular; NAFLD, Nonalcoholic fatty liver disease; RHI, arterial tonometry index; SAA-LDL, serum amyloid A-LDL; SDF-1alpha, stromal derived factor-1α; $sPLA_2$, secreted phospholipase-A_2; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-α; TC, total cholesterol; TG, Triglyceride; VLDL, Very low density lipoprotein

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https://doi.org/10.1016/j.vph.2018.05.010
Received 12 December 2017; Received in revised form 15 March 2018; Accepted 30 May 2018
1537-1891/

Table 1
Currently approved DPP-4 inhibitors.

Drug	Time to market	Manufacturer	Recommended dosages
Sitagliptin	2006	Merck & Co	100 mg once daily
Vildagliptin	2007	Novartis	50 mg once or twice daily
Saxagliptin	2009	Bristol-Myers Squibb and AstraZeneca	5 mg once daily
Linagliptin	2011	Boehringer Ingelheim and Lilly	5 mg once daily
Gemigliptin	2012	LG Life Sciences and Double-Crane Pharmaceutical Co	50 mg once daily
Anagliptin	2012	Sanwa Kagaku Kenkyusho Co., Ltd. and Kowa Company, Ltd.	100 mg twice daily
Teneligliptin	2012	Mitsubishi Tanabe Pharma and Daiichi Sankyo	20 mg once daily
Alogliptin	2013	Takeda Pharmaceutical Company	25 mg once daily
Trelagliptin	2015	Takeda Pharmaceutical Company	100 mg once weekly

1.1. Anti-inflammation in atherosclerosis

Inflammation has been identified as a key etiological factor in the development of atherosclerosis and cardiovascular diseases [9]. Biomarkers of inflammation including hsCRP, IL-1β, IL-6, IL-18, and TNF-α et al., have beeninvolved in the initiation and progression of atherosclerosis. DPP-4, also known as CD26, is expressed on the membranes of various cells including leukocytes, mediating proinflammatory signals [10]. The activity of DPP-4 is a major predictor of the onset of inflammation and atherosclerosis [11]. A number of experimental studies have explored the specific signaling pathways by which DPP-4 inhibitors may counteract inflammation [12–14]. Recently, the evidence from clinical studies has further confirmed the effect of anti-inflammation of DPP-4 inhibitors in humans. (Table 2).

DPP-4 inhibitor sitagliptin has been found to be associated with anti-inflammation process in several trials. A single center, randomized, placebo-controlled, double-blinded prospective study showed that sitagliptin had a potent and rapid anti-inflammatory effect by suppressing the expression of CD26 as well as its activity, consequently reducing the expression of inflammatory genes and the concentrations of CRP and IL-6 in type 2 diabetes [15]. Similar results were observed in a 48 patients enrolled trial showing that treatment with sitagliptin for 3 months reduced levels of SAA-LDL and pro-inflammatory cytokines, such as CRP and TNF-α, while increased the level of an anti-inflammatory cytokine, IL-10,both in serum and peripheral blood monocytes in T2DM patients [16]. In another placebo-controlled study, treatment with sitagliptin (100 mg/d) for 6 weeks significantly reduced levels of inflammatory markers, mainly CRP, IL-6, IL-18, $sPLA_2$ in T2DM patients [17]. As added-on therapy to glimepiride, 24-week treatment with sitagliptin significantly reduced the serum level of sCD163, which can be used as a marker for activated macrophages compared with α glucosidase inhibitor [19]. Moreover, sitagliptin was also found to have beneficial anti-inflammatory effects in HIV infected adults with impaired glucose tolerance [18].

Besides sitagliptin, there are some other DPP-4 inhibitors showing the same anti-inflammatory potential. In patients with T2DM, the addition of vildagliptin led to a significant suppression of the IL-1ß and hsCRP elevation compared with metformin alone [20, 21]. In patients with T2DM receiving metformin treatment, therapy with vildagliptin for 6 months showed a stronger impact on lowering the levels of IL-6, hsCRP and TNF-α compared with glimepiride during the oral fat load test [22]. A prospective, randomized, open-label trial was conducted to evaluate the effect of two DPP-4 inhibitors,vildagliptin and sitagliptin, on systemic inflammation markers in type 2 diabetic patients. The effect of the reduction of systemic inflammation markers had been found greater in the vildagliptin group than in the sitagliptin group [23]. Similarly, DPP-4 inhibitor linaliptin monotherapy for 6 months significantly decreased the level of IL-6 in hemodialysis patients with diabetes [25]. The favorable effect of linagliptin in T2DM patients on inflammation has also been verified by another randomized, placebo-controlled trial [24].

1.2. Endothelial cell function improvement

Dysfunction of the endothelial lining of lesion-prone areas of the arterial vasculature is an important contributor to the pathobiology of atherosclerotic cardiovascular disease [26]. GLP-1 could induce an endothelial-dependent relaxation via NO-dependent action, which will help to enhance endothelial cell function [27]. Besides, vasculoprotective endothelial progenitor cells (EPCs) are regulated by SDF-1α, which is a substrate of DPP-4. DPP-4 inhibitors increase EPCs with concomitant upregulation of SDF-1α indicating this class of drug might play an significant role in endothelial cell biology [28]. In several recent randomized trials, both short-term and long-term treatment with DPP-4 inhibitors could increase the number of circulating EPCs when compared with placebo or other antihyperglycemic drugs [29–32]. To evaluate endothelial function, ultrasound measurements of FMD are the most widely used non-invasive vascular test [33, 34].

Numerous clinical trials have indicated the positive impact of DPP-4 inhibitors on endothelial cell function. A randomized, double-blind, placebo-controlled trial with 40 patients enrolled demonstrated that 12-week treatment with linagliptin tended to improve endothelial and neurovascular microvascular function in patients with T2DM [24]. Similarly, in the study byJax et al., under fasting conditions, treatment with linagliptin for 4 weeks significantly improved microvascular function as shown by a 34% increase in hyperaemia area, a 34% increase in resting blow flow, as well as a 25% increase in peak blood flow [35]. In patients with T2DM treated with metformin, the addition of linagliptin significantly improved FMD from baseline compared with addition of metformin [36]. In another randomized trial, 62 patients with T2DM were assigned to receive either linagliptin 5 mg or placebo for 4 weeks. Although renal plasma flow (RPF) did not change after treatment with linagliptin or placebo, the change in RPF due to L-NMMA, a blocker of NOS, was smaller in the linagliptin group, indicating a lower basal NO activity after treatment with linagliptin [37]. In another pilot study, treatment with trelagliptin for 12 weeks was found no significant changes in FMD. But the result turned out a significant up-regulation of serum adiponectin level, which can enhance the production of NO. [38] Sagara et al. conducted a randomized trial to elucidate the effect of teneligliptin, another drug of DPP-4 inhibitors, on endothelial function. 45 patients with T2DM and CKD treated with sitagliptin, were randomized to either continue sitagliptin or switch to teneligliptin for 24 weeks. Treatment with teneligliptin, but not sitagliptin, improved endothelial function valued by reactive hyperaemia index [39]. In the study by Hashikita et al., twenty-nine T2DM patients not receiving any incretin-based drugs were prescribed with teneligliptin for 3 months. Compared with baseline levels, there represented an improvement in endothelial function assessed by RH-PAT index [40]. In addition, 1-week treatment of 25 mg/day alogliptin was found significantly improving postprandial endothelial dysfunction tested by %FMD in healthy people [41].

The improvement of sitagliptin on endothelial cell function was also confirmed by many, but not all clinical trials. Fadini et al. reported that a 4-week therapy with 100 mg oral sitagliptin increased plasma SDF-1α