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Review

DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials

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Abstract

Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes. Direct comparisons with active glucose-lowering comparators in drug-naive patients have demonstrated that DPP-4 inhibitors exert slightly less pronounced HbA_{1c} reduction than metformin (with the advantage of better gastrointestinal tolerability) and similar glucose-lowering effects as with a thiazolidinedione (TZD; with the advantage of no weight gain). In metformin-treated patients, gliptins were associated with similar HbA_{1c} reductions compared with a sulphonylurea (SU; with the advantage of no weight gain, considerably fewer hypoglycaemic episodes and no need for titration) and a TZD (with the advantage of no weight gain and better overall tolerability). DPP-4 inhibitors also exert clinically relevant glucose-lowering effects compared with a placebo in patients treated with SU or TZD (of potential interest when metformin is either not tolerated or contraindicated), and as oral triple therapy with a good tolerability profile when added to a metformin–SU or pioglitazone–SU combination. Several clinical trials also showed a consistent reduction in HbA_{1c} when DPP-4 inhibitors were added to basal insulin therapy, with no increased risk of hypoglycaemia. Because of the complex pathophysiology of type 2 diabetes and the complementary actions of glucose-lowering agents, initial combination of a DPP-4 inhibitor with either metformin or a glitazone may be applied in drug-naive patients, resulting in greater efficacy and similar safety compared with either drug as monotherapy. However, DPP-4 inhibitors were less effective than GLP-1 receptor agonists for reducing HbA_{1c} and body weight, but offer the advantage of being easier to use (oral instead of injected administration) and lower in cost. Only one head-to-head trial demonstrated the non-inferiority of saxagliptin *vs* sitagliptin. Clearly, more trials of direct comparisons between different incretin-based therapies are needed. Because of their pharmacokinetic characteristics, pharmacodynamic properties (glucose-dependent glucose-lowering effect) and good overall tolerability profile, DPP-4 inhibitors may have a key role to play in patients with renal impairment and in the elderly. The role of DPP-4 inhibitors in the therapeutic armamentarium of type 2 diabetes is rapidly evolving as their potential strengths and weaknesses become better defined mainly through controlled clinical trials.

Keywords: Clinical trial-DPP-4 inhibitor; Alogliptin; Linagliptin; Saxagliptin; Sitagliptin; Vildagliptin; Type 2 diabetes mellitus; Review

Résumé

Les inhibiteurs de la DPP-4 dans le traitement du diabète de type 2 : revue critique des essais cliniques contrôlés.

Les inhibiteurs de la dipeptidylpeptidase-4 (DPP-4) offrent de nouvelles options pour le traitement du diabète de type 2. Des comparaisons directes avec d'autres médicaments antidiabétiques chez des patients naïfs de tout traitement ont démontré que les inhibiteurs de la DPP-4 étaient un peu moins puissants pour diminuer le taux d'HbA_{1c} que la metformine (avec l'avantage d'une meilleure tolérance digestive) et aussi puissants que les thiazolidinediones (avec l'avantage d'une neutralité pondérale). Chez les patients déjà traités par metformine, les gliptines entraînent une baisse des taux d'HbA_{1c} similaire à celle observée avec les sulfamides (mais sans prise de poids, sans hypoglycémie et sans nécessité de titration) ou avec les thiazolidinediones (avec l'avantage de l'absence de prise de poids et d'un meilleur profil de tolérance). Les inhibiteurs de la DPP-4 améliorent aussi le contrôle glycémique par rapport à un placebo chez les patients traités avec un sulfamide ou une thiazolidinedione (ce qui peut être intéressant chez les patients pour lesquels la metformine est non tolérée ou contre-indiquée) ou encore en triple thérapie orale en étant ajoutés à une combinaison metformine-sulfamide ou pioglitazone-sulfamide, avec toujours un bon profil de tolérance. Plusieurs essais cliniques ont montré une diminution consistante des taux d'HbA_{1c} lorsqu'un inhibiteur de la DPP-4 était ajouté à une insulinothérapie basale,

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sans accroître le risque d'hypoglycémie. En raison de la physiopathologie complexe du diabète de type 2 et de la complémentarité d'action des médicaments hypoglycémiants, une combinaison initiale d'un inhibiteur de la DPP-4 avec soit la metformine, soit une glitazone peut être proposée chez les patients insuffisamment contrôlés par régime et exercice, avec une meilleure efficacité et une aussi bonne tolérance qu'une monothérapie pharmacologique initiale. Les inhibiteurs de la DPP-4 sont moins efficaces que les agonistes des récepteurs du *glucagon-like peptide-1* en ce qui concerne la diminution des taux d'HbA_{1c} et du poids, mais offrent le bénéfice d'un usage plus facile (prise orale au lieu d'une injection) et d'un coût moins élevé. Un seul essai clinique comparatif direct a été publié à ce jour entre deux inhibiteurs de la DPP-4, démontrant une non infériorité de la saxagliptine par rapport à la sitagliptine. De toute évidence, davantage d'essais cliniques devraient offrir une comparaison directe entre les différents traitements fondés sur l'effet incrétine. En raison de leurs caractéristiques pharmacocinétiques, de leurs propriétés pharmacodynamiques (effet hypoglycémiant glucose-dépendant) et de leur bon profil de tolérance, les gliptines devraient occuper une place de choix chez les patients avec une insuffisance rénale ou chez les sujets âgés. Le rôle des inhibiteurs de la DPP-4 dans l'arsenal thérapeutique du diabète de type 2 évolue rapidement au fur et à mesure que leurs avantages et inconvénients apparaissent mieux définis, essentiellement grâce aux essais cliniques contrôlés.

Mots clés : Diabète de type 2 ; Essai clinique ; Inhibiteur de la DPP-4 ; Alogliptine ; Linagliptine ; Saxagliptine ; Sitagliptine ; Vildagliptine ; Revue générale

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a novel pharmacological class of glucose-lowering agents that open up new perspectives for the management of type 2 diabetes mellitus (T2DM). The mechanism of action of DPP-4 inhibitors is distinct from any existing class of oral glucose-lowering agents [1]. Although they are not more potent in lowering blood glucose concentrations and reducing glycated haemoglobin (HbA_{1c}) levels [2], DPP-4 inhibitors nevertheless offer several clinically relevant advantages [3–5]. Among the most important benefits are a negligible risk of hypoglycaemia that is considerably lower than that observed with sulphonylurea (SU), and a weight-neutral profile in contrast to the weight gain generally observed with SU and thiazolidinedione (TZD). DPP-4 inhibitors have been evaluated as monotherapy and in various combinations with other glucose-lowering agents, and compared with either a placebo or an agent of another glucose-lowering pharmacological class as an active comparator [6].

The present review is an updated evaluation of five DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin) in randomized clinical trials in the literature so far, and focuses particularly on the following topics:

- direct comparisons with active glucose-lowering comparators in drug-naive or metformin-treated patients;
- comparisons with placebo or active comparators in more unusual indications as an add-on to SU or TZD, as oral triple therapy or as an add-on to insulin;
- use as the initial combination with metformin or TZD in drug-naive patients;
- comparisons with glucagon-like peptide-1 (GLP-1) receptor agonists or other gliptins in head-to-head trials;
- use of DPP-4 inhibitors in special populations, especially patients with renal impairment and the elderly.

2. Methods

To identify the relevant studies, an extensive literature search of Medline was performed from January 2005 to August 2011, using the term "DPP-4 inhibitors", and the generic names "sitagliptin", "vildagliptin", "saxagliptin", "alogliptin" and "linagliptin". No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined. Only clinical trials that randomized at least 100 T2DM patients and lasted at least 12 weeks were considered. Most of the studies ran for 24–26 weeks, with a maximum follow-up duration of 104 weeks in a few cases.

3. Results

3.1. Gliptins as monotherapy or as add-ons to metformin

Numerous placebo-controlled trials have demonstrated both the efficacy and safety of DPP-4 inhibitors in patients with T2DM treated with diet and exercise (drug-naive patients), and in patients treated with metformin monotherapy, the first-line drug choice for T2DM. All of these trials showed that DPP-4 inhibitors reduced HbA_{1c}, fasting plasma glucose and postprandial glucose levels without inducing hypoglycaemia, with near weight neutrality and a tolerability profile that did not differ from that of placebo. These trials have already been summarized in various reviews [7] and meta-analyses [2,8]. Clinically relevant reductions in HbA_{1c} were obtained with a gliptin across a wide range of T2DM patient subgroups examined by either specific baseline demographic characteristics or β-cell function indices such as the homoeostatic model assessment (HOMA)-β [9]. Our present report has specifically compared DPP-4 inhibitors with active glucose-lowering comparators (instead of a placebo) to better delineate the potential advantages (and disadvantages) of DPP-4 inhibitors in clinical use.

3.1.1. Gliptins as monotherapy

As metformin is considered the first-line drug therapy for the management of T2DM [10,11], it is of interest to compare the efficacy (and safety) of a DPP-4 inhibitor with that of metformin in drug-naive T2DM patients insufficiently controlled with diet and exercise [12–21]. Overall, metformin (1000–2000 mg/day) demonstrated slightly (but significantly) greater reductions in both HbA_{1c} and body weight (Table 1, Fig. 1). However, the DPP-4 inhibitor showed superior gastrointestinal tolerability compared with metformin. Nevertheless, these comparative results do not support the initial use of a DPP-4 inhibitor instead