Dipeptidyl Peptidase Inhibitors: A New Step Towards Normoglycemia

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Abstract: Current medical therapy of type 2 diabetes use drugs targeting either insulin resistance, as metformin and/or glitazones, or insulin secretion, as sulfonylureas or glinides. The incretin effect, mainly due to glucagon-like peptide 1 (GLP-1), enhances the post-meal secretion of insulin, but its potential pharmacological use is hampered by the very short half-life of GLP-1. The inhibition of dipeptidyl peptidase-4 (DPP-4), which inactivates GLP-1, has led to the development of a new class of antidiabetic molecules, the DPP-4 inhibitors, also known as gliptins. Sitagliptin is now commercially available, but many other gliptins are currently under clinical development. Their normoglycemic efficacy is moderate, with a mean HbA1c decrease by 0.7 to 1.1%, and they are well-tolerated, especially with a low risk of hypoglycaemia and no weight gain. In animal studies, they appear to preserve pancreatic β-cell function, by increasing β-cell mass and reducing apoptosis. The clinical significance of these properties requires confirmation by further long-term studies. DPP-4 inhibitors seem to represent an efficient and well-tolerated new class of oral normoglycaemic agents, with a potential beneficial effect on pancreatic function, but their real efficacy and safety have to be firmly assessed in the future, before they could find their appropriate place in the management of type 2 diabetes.

Keywords: Dipeptidyl peptidase-4 inhibitors, incretin, metformin, sitagliptin, type 2 diabetes, vildagliptin.

INTRODUCTION

The burden of type 2 diabetes is rapidly rising throughout the world, and this will undoubtedly dramatically increase morbidity and mortality due to micro- and macrovascular complications. This evolution is due not only to genetic predisposition, but mainly to contemporary lifestyle which favours sedentarity and abundance of high-fat and high-carbohydrate diet. Homeostasis of blood glucose level is maintained through balanced secretion of insulin and glucagon, synthesized respectively by β and α cells of the pancreatic islets. Pathophysiology of type 2 diabetes is characterized by a combination of insulin resistance and failure of insulin secretion. At early stage of the disease and even before, in the prediabetic state, insulin resistance is the predominant abnormality, but it is compensated by an increase in insulin secretion, in order to keep glycaemia in the normal range. As time goes by, this compensation disappears because insulin secretion begins to fail, which leads to overt diabetes. To date, main available oral antidiabetic medications target either insulin resistance (metformin, glitazones), or insulin deficiency (sulfonylureas, glinides). A new approach is the use of agents that enhance the physiological activities of gut-derived hormones known as incretins.

1. The Incretin Effect (Fig. 1A)

After glucose intake, the secretion of insulin varies depending on the route of glucose administration. Oral glucose provides a more potent insulinotropic stimulus compared with isoglycaemic intravenous challenge. This finding is known as incretin effect [1] and is mainly due to two peptides, GIP (glucose-dependent insulinotropic peptide, formerly known as gastric inhibitory peptide), and GLP1 (glucagon-like peptide-1), which seems to be responsible for the major part of incretin effect on β-cell function [2] and hence has become the favourite potential therapeutic candidate. Moreover, diabetic patients appear to be resistant to GIP while they have reduced GLP1 secretion but normal responsiveness to the hormone. GLP1 enhances insulin secretion only when glucose level rises above 5 mmol/l [3]. Incretins have no longer insulinotropic effect when blood glucose level decreases below 3 mmol/l.

GLP1 is a 37 aminoacid polypeptide secreted in L-type endocrine cells of the distal ileum and colon. A meal rich in fat and carbohydrates is the main physiological stimulus for GLP1 secretion. It is released into the circulation quickly after oral ingestion, in a biphasic pattern (early phase within 10 to 15 mn, and second phase within 30 to 60 mn). The early release is likely to be mediated by autonomic nervous system, by neurotransmitters as acetylcholine, and by GIP. Conversely the second phase of GLP1 secretion is mediated by direct contact of nutrients with the L cells [4]. In humans, major part of circulating GLP1 is GLP1(7-36) amide.

The circulating level of GLP1 is rapidly decreasing after secretion (half-life < 2 min) because of enzymatic inactivation mainly due to dipeptidyl-peptidase 4 (DPP-4), which cleaves GLP1 into the inactive form GLP1(9-36) amide.

Consequently, as inhibition of DPP-4 increases the half-life of incretins, it has become a new target in the development of normoglycaemic molecules.

2. Enzyme Dipeptidyl Peptidase 4

DPP-4 is an ubiquitous enzyme, broadly found in numerous tissues, which belongs to the serine protease family. It is also found in vascular endothelial cells and

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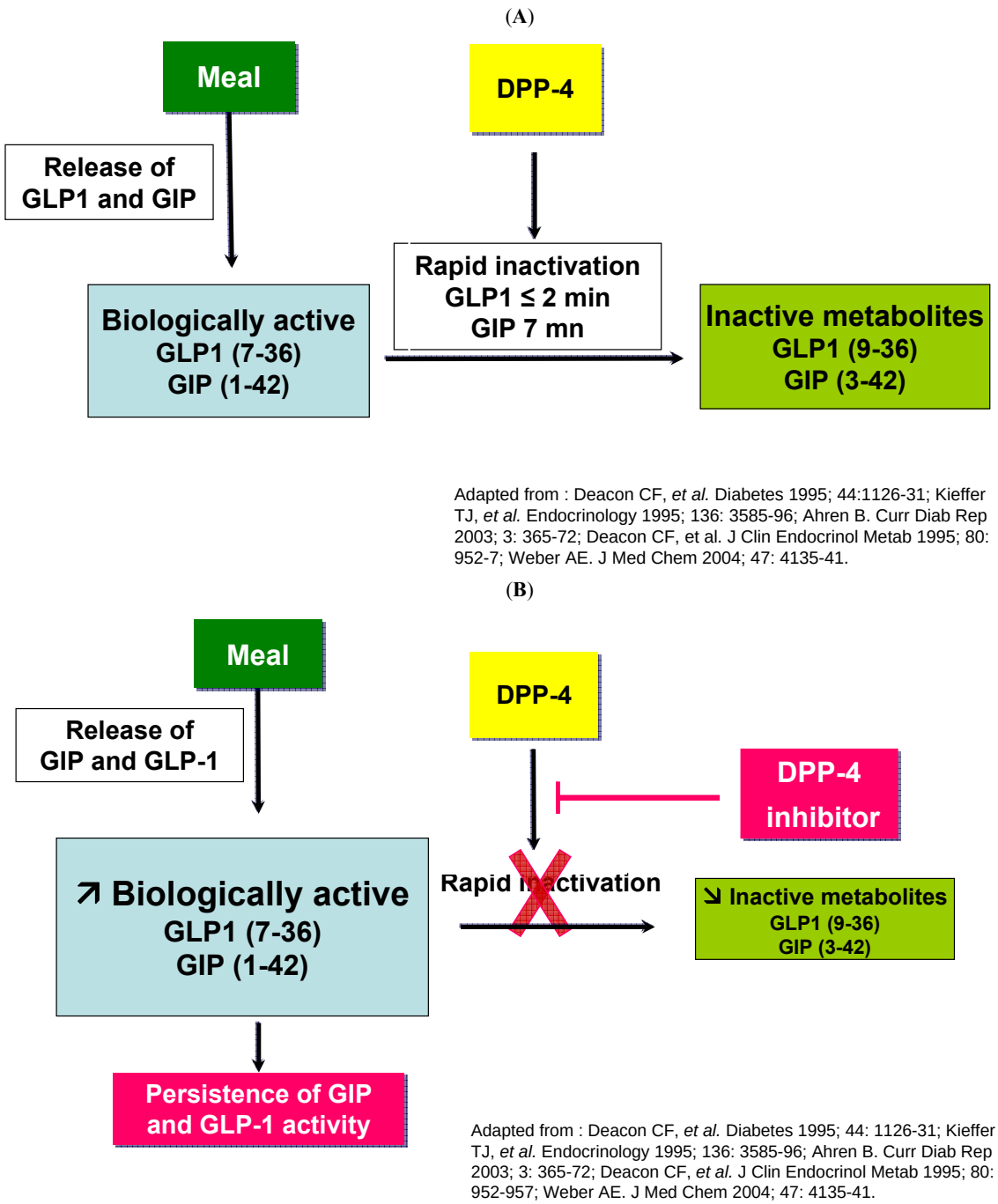

Fig. (1). (**A**) Secretion and action of incretins. (**B**) Mechanism of action of DPP-4 and gliptins on incretin system.

immune-related cells (DPP4 is identical to CD26, a marker of activated T-cells). It is a 766 amino-acid proline peptidase which cleaves peptides after a proline residue. The human gene has been located to locus 2q24.3 on chromosome 2 [5]. It cleaves a large number of peptides *in vitro*, but *in vivo* few peptides are endogenous physiological substrates for the enzyme. Both GIP and GLP-1 are substrates for DPP-4, and genetic inactivation of the enzyme in animal results in better glucose tolerance. Pharmacological inhibition of DPP-4 results first in increased level of GIP and GLP-1, then in decreased blood glucose, *via* both enhanced insulin secretion and decreased glucagon release (Fig. **1B**). But DPP-4 is the founding member of an enzymatic family whose members are linked by their common cleaving serine dipeptidyl peptidase mechanism. Two other human dipeptidases, DPP-8 and DPP-9, display structures closely related to DPP-4, but their precise roles remain unknown. Indeed, in animal models (rats and dogs) inhibition of DPP-8 and DPP-9 results in various tissue toxicity : splenomegaly and lymphadenopathy, gastrointestinal mortality with multiorgan pathology. Moreover, inhibition of DPP-8/9 appears to reduce T-cell activation in human *in vitro* models [6]. So it seems very important to assess the degree of selectivity for DPP-4 of inhibitors in clinical development: they should be highly selective for DPP-4 and unselective for DPP-8/9.

3. Pharmacological DPP-4 Inhibitors

a. General data

Actually, several DPP-4 inhibitors are under clinical development (Table **1**). The two most advanced are sitagliptin (MSD), which is actually commercially available, and vildagliptin (Novartis), which has been approved by the European Medicine Agency for use within the european countries (Table **2**). Two other drugs are currently under advanced development, saxagliptin (BMS), and alogliptin (Takeda). They can be orally administered, and their prolonged delay of action allows a once-daily administration. They inhibit DPP-4 activity by almost 100%, 30 minutes after oral administration, and 80% of this inhibition (which results in 2 to 3-fold increase in active GLP-1 levels) lasts about 16h [7]. The daily dose is 100 mg for both. In case of hepatic insufficiency they do not require dose adjustment, but renal failure can increase plasma level of gliptins, thus their dose has to be adjusted according to creatinine clearance: patients with mild renal insufficiency do not require dose adjustment, but dose reduction may be mandatory in patients with more severe renal impairment. Neither gender nor obesity requires dose adaptation [8].

b. Metabolic Effects

The global normoglycemic effect of gliptins is a decrease of HbA1c in a range of 0.4 to 1.1% (mean difference 0.74%), with minor differences between molecules [9]. In monotherapy, gliptins result in a reduction in HbA1c value of 0.5 to 0.9% versus placebo. Improvement of glycaemic control is more pronounced in patients with the highest HbA1c levels at baseline. This improvement is mainly due to a reduction in post-prandial hyperglycaemia, rather than in fasting glucose level. Regarding the overall effect of gliptins on body weight, it is important to note that it is neutral. There was a slight weight increase with gliptins compared to placebo (+ 0.5 kg). Compared to glipizide, sitagliptin showed a favourable effect (- 2.5 kg versus + 1.0 kg) [10], so did vildagliptin versus rosiglitazone [11] or versus pioglitazone [12], but weight loss was greater with metformin compared to vildagliptin [13].

Table 1. Development Status of DPP-4 Inhibitors (Update October 2008)

Company	Product Name/Code	Development Status
MSD	Sitagliptin	Approved: FDA Oct 06 EMEA March 07
Novartis	Vildagliptin	Approved : EMEA Sept 07
Takeda	Alogliptin	Phase 3 Submitted FDA Jan 08
BMS	Saxagliptin	Phase 3
Boehringer Ingelheim	BI-1356	Phase 2
Prosidion	PSN 9301 PSN 357	Phase 2 Phase 1
Roche	R 1498 R 1499	Phase 2 Phase 1
Lilly	TS-021	Phase 1

MSD: Merck-Sharp and Dohme
BMS: Bristol-Myers-Squibb
FDA: Food and Drug Administration
EMEA : European Medicines Agency
Adapted from Galtier F. Med Mal Metab 2008; 2(suppl 1): S38-S41.

Table 2. Comparison of the Currently Available DPP-4 Inhibitors

	Sitagliptin	Vildagliptin
Mechanisms of action	Increase of GLP1 level Increase of insulin secretion Decrease of glucagon secretion Preservation of β-cell mass (*in vitro*)	
Development status	Currently available	
Reduction of HbA1c **- monotherapy** **- in combination with metformin**	 0.6-0.8% 0.6-0.8%	 0.4-1.2% 1.1%
Effect on weight	Neutral	
Side effects	Upper respiratory tract infections Headaches	
Hypoglycaemias	Comparable to placebo	
Lipids	No effect on fasting levels	No effect on fasting levels Reduction of postprandial triglyceride levels
Precautions for use	Caution in patients > 75 years Use not recommended if creatinine clearance < 50 ml/mn	
Drug interactions	None	

Gliptins have no or little effect on fasting plasma lipid levels. However, it has been shown that vildagliptin can reduce postprandial triglyceride-rich lipoproteins [14].

Direct comparison is not possible between gliptins, because no head-to-head study has been performed to date.

c. Sitagliptin

Sitagliptin can fully inhibit DPP-4 at a dose range between 50 and 400 mg/day. When used as monotherapy, a 100 mg daily dose decreases HbA1c in a range of 0.60 to 0.79%) [15]. A similar action has been found when used in combination with metformin [16] or pioglitazone [17]. Gastro-intestinal tolerance was good, there were no more hypoglycaemia with sitagliptin compared to placebo, and weight remained stable throughout the studies. In the meta-analysis performed by Amori *et al.* [9], HbA1c levels in the different sitagliptin studies varied from +0.04% to -1.05%. In the seven studies comparing sitagliptin to placebo, which gathered 2404 patients, the mean change of HbA1c was -0.74%. Risk ratio of adverse events (hypoglycaemia, nausea, vomiting, diarrhea, abdominal pain, cough, influenza) was not significantly different between sitagliptin and comparator.

d. Vildagliptin

After 4 weeks of treatment with 100 mg/d, vildagliptin inhibits selectively DPP-4 more than 90%. It is excreted by both digestive and urinary route. Its half-life is shorter than sitagliptin (1.7 *vs* 12 h). Its action is yet extended in spite of this fast elimination. In monotherapy, it decreases HbA1c in a range of 0.4 to 1.2% *vs* placebo [18, 19]. In combination therapy, the decrease of HbA1c was of 1.1% when vildagliptin was added to metformin [20], and of 1.0% when added to pioglitazone [21]. In the meta-analysis from Amori *et al.* [9], HbA1c levels in the different vildagliptin studies varied from +0.40% to -1.20%. In the nine studies comparing vildagliptin to placebo, which gathered 1786 patients, the mean change of HbA1c was -0.73%. Vildagliptin has also been added to insulin [22]: in the combination group compared to the group given insulin alone, mean HbA1c level was reduced by 0.5% *vs* 0.2%, and hypoglycaemias were less frequent (113 events in 33 patients versus 185 events in 45 patients).

e. Saxagliptin

To date, few clinical data regarding saxagliptin are available. In a 12-week placebo-controlled trial, 338 drug-naïve type 2 diabetic patients (low-dose cohort) with inadequate glycaemic control (HbA1c between 6.5 and 9.7%) were randomized between different doses of saxagliptin (2.5, 5, 10, 20 or 40 mg/day) or placebo. Mean HbA1c level was reduced by 0.7 to 0.9%, versus 0.3% for placebo. In a second cohort (high-dose cohort), 85 diabetic patients were randomized between saxagliptin 100 mg daily and placebo for 6 weeks; HbA1c was reduced by 1.1%, versus 0.4% in the placebo group. In both cohorts, weight did not significantly change compared to placebo, and incidence of confirmed hypoglycaemias was very low [23].

f. Alogliptin

When used as monotherapy in type 2 diabetic patients for 26 weeks [24], alogliptin significantly reduced HbA1c level [-0.70% (12.5 mg/day), -0.91% (25 mg/day)], compared to patients receiving placebo (-0.15%). The effect on weight was neutral (12.5 mg/day: -0.09 kg, 25 mg/day: -0.22 kg, placebo: +0.18 kg). In diabetic patients inadequately controlled on metformin monotherapy [25], mean HbA1c value was also significantly reduced (-0.6% for both doses 12.5 and 25 mg/day) compared to the placebo group (-0.1%). When used in add-on to glyburide monotherapy [26], in diabetic patients, alogliptin reduced HbA1c levels at 26 weeks [-0.38% (12.5 mg/day), -0.52% (25 mg/day)], compared to patients receiving placebo (+0.01%). When alogliptin is added to pioglitazone therapy in type 2 diabetic patients inadequately controlled on glitazone alone or on glitazone with metformin or sulfonylurea [27], HbA1c is reduced significantly in alogliptin patients [-0.66% (12.5 mg/day), -0.80% (25 mg/day)], compared to patients receiving placebo (-0.19%). No significant differences were found in weight. Finally, when alogliptin is added to insulin in patients with type 2 diabetes incompletely controlled on insulin alone or on insulin with metformin [28], mean HbA1c level is reduced [-0.63% (12.5 mg/day), -0.71% (25 mg/day)], compared to patients receiving placebo (-0.13%).

g. Adverse Effects

Both sitagliptin and vildagliptin appear to be well-tolerated and safe, with a rate of adverse events similar to comparator. Hypoglycaemias are rare, because GLP-1 action is glucose-dependent: in the meta-analysis from Amori *et al.* [9], the risk of hypoglycaemia is not significantly different in patients treated with DPP-4 inhibitors *vs* comparators (RR 0.97, CI 95%: 0.50-1.86). However hypoglycaemias can be observed when a gliptin is combined with insulin or insulin secretagogue. Many studies report no effect on blood pressure, although a slight decrease has been noted in one study using vildagliptin [20]. A major topic in the use of DPP-4 inhibitors is their neutral influence on body weight. This is different from metformin, which is generally associated with slight decrease in body weight, and from the weight gain due to use of glitazones and insulin secretagogues. Studies with gliptins have reported no gastrointestinal side effect compared to placebo. Amori *et al.*, in their meta-analysis [9], showed an increased risk of infections, such as nasopharyngitis and urinary tract infections. These observations might be explained by the ubiquity of DPP-4, which is expressed in various tissues, including immune tissues and lymphocytes. Also known as CD26 on T-cells, DPP-4 contributes to T-cell activation and proliferation. Thus it is possible that pharmacologic inhibition of DPP-4 by gliptins, especially if not selective enough, could interfere with the immune function [29].

h. Potential Effects on β-Cell Function

As the normal mass of pancreatic β-cells is tightly maintained stable between growth and apoptosis, it is critical to assess whether DPP-4 inhibitors are able to prevent or delay the decline of β-cell pancreatic function, which has been shown to progress with time in type 2 diabetes. There are experimental arguments in rodents to support that gliptins could preserve islet cell function and could improve β-cell survival, with reduced apoptosis. In streptozotocin-induced diabetic mice, sitagliptin seems to preserve β-cell mass [30]; in neonatal rats, vildagliptin increases the mass

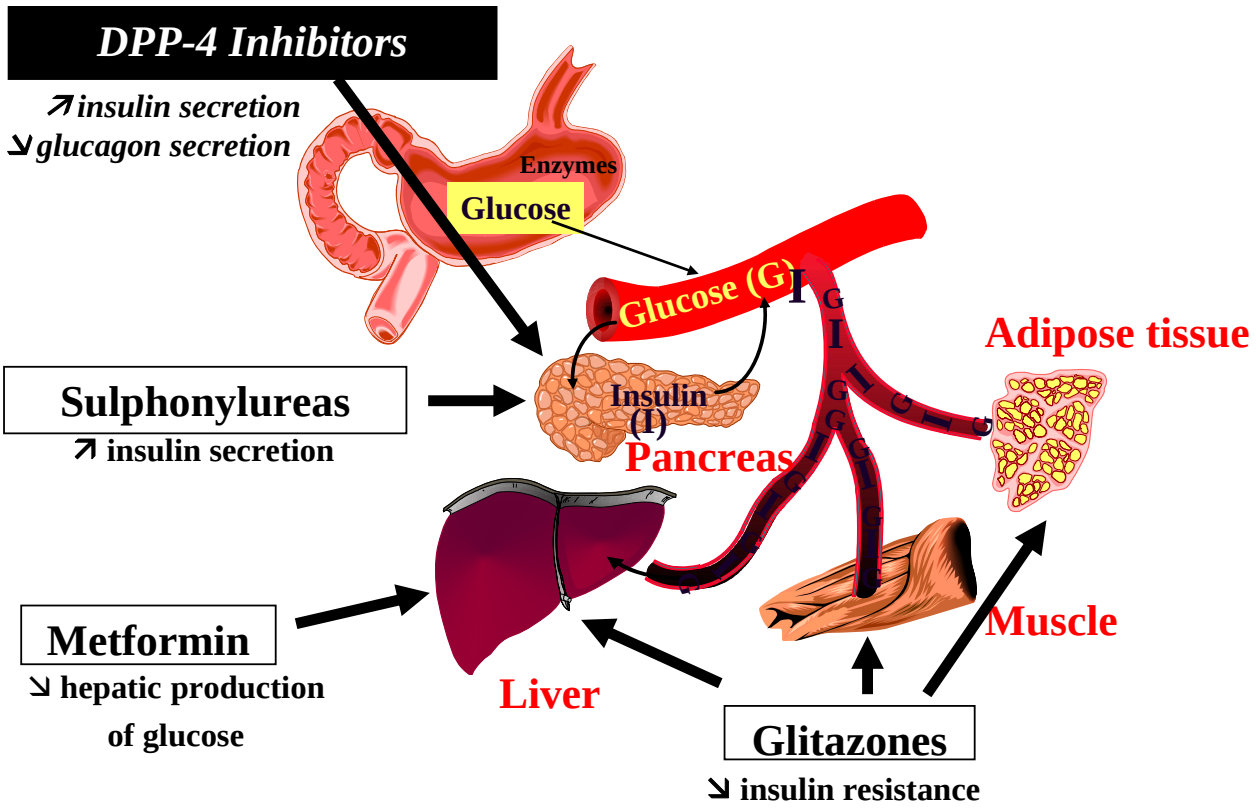

Fig. (2). Targets and mechanisms of action of oral hypoglycaemic agents.

and decrease the apoptosis of β-cell [31]. These observations deserve further confirmation in humans.

4. Position of DPP-4 Inhibitors in the Pharmacological Management of Type 2 Diabetes

The use of sitagliptin is now approved for the treatment of type 2 diabetes poorly controlled by diet and monotherapy, or in combination with metformin or glitazone when glycaemic control is inadequate. The recommended daily dose is 100 mg, without any adjustment according to age, hepatic insufficiency, or mild to moderate renal failure. In case of more severe renal failure, the sitagliptin dose has to be reduced to 50 mg/d if creatinine clearance ranges from 50 to 30 ml/min, and to 25 mg if clearance is less than 30 ml/min. From a broader point of view, taken into account their good tolerance, low frequence of hypoglycaemia, neutral effect on body weight, and low occurrence of drug interactions, gliptins in type 2 diabetes could replace insulin secretagogues as second or third step add-on option after first-line metformin therapy, or after second-line metformin-glitazone combined treatment. They could be considered also in combination with insulin, but available data to date regarding this latter option are scarce. Although studies about combination of gliptins and sulfonylureas are going on, efficiency of such an association remains to be established, particularly concerning its cost-effectiveness and the risk of hypoglycaemia. In the ADA/EASD consensus statement [32], gliptins are not included in the algorithm for initiation and adjustment of management of hyperglycaemia, owing to their lower or equivalent overall glucose-lowering effectiveness compared with the well-validated therapies and/or to their limited clinical data or relative expense.

CONCLUSION

Treatment with DPP-4 inhibitors (gliptins) provides a new approach in the management of type 2 diabetes with oral therapy (Fig. **2**). In individual studies, gliptins seem to display moderate normoglycaemic potency when compared to currently available antidiabetic drugs, but they are safe and well-tolerated, with rare hypoglycaemias, neutral effect on body weight, and no significant drug interaction. Anyway, we need further controlled studies to assess whether the potential β-cell protective property could be confirmed in the long-term, and would provide sustainable effects on glycaemic control. It will be also mandatory to watch for possible pancreatic tumorigenesis, as gliptins claim a new balanced action between stimulation of β-cell mass and reduction of apoptosis. Regarding safety issues, some uncertainty persists about eventual unfavourable side effects concerning the immune system. This concern might be overcome by increasing the selectivity for DPP-4 of commercially available inhibitors in the future.

ABBREVIATIONS

GLP-1 = Glucagon-like peptide 1

DPP-4 = Dipeptidyl peptidase 4

GIP = Glucose-dependent insulinotropic peptide

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