DPP-4 inhibitors and GLP-1 analogues: for whom?
Which place for incretins in the management of type 2 diabetic patients?

S. Halimi
Department of Endocrinology Diabetology Nutrition, University Hospital Grenoble, F-38043 Grenoble, France

Abstract

This review tries to delineate how to insert the GLP-1 based agents, DPP4-inhibitors (sitagliptin and vildagliptin) and GLP-1 analogues (exenatide and liraglutide), in the guidelines and the daily practice for the management of type 2 diabetes (T2DM). Orally administered DPP-4 inhibitors reduce HbA1c by 0.5-1.1%, without hypoglycaemic events and no weight gain. The subcutaneous injected GLP-1 analogues show larger reductions in HbA1c by 0.8-1.7% and a weight loss (1.75-3.8 kg) with most gastrointestinal common adverse events contributing to a significant treatment interruption. Regarding the efficacy, the cost and the safety of these drugs they will not challenge the use of metformin as the initial therapy of T2DM. In patients’ not tolerating metformin or in older patients, DPP-4 inhibitors seem to be an excellent alternative monotherapy. Several studies argue in favour of the use of DPP-4 inhibitors in combination with metformin as a promising second line treatment. This combination offers advantages when compared to others currently used, particularly if one considers the more stringent guidelines with a higher risk of hypoglycaemic events in patient receiving sulfonylureas and mild hyperglycaemia or weight gain with thiazolidinedione (TZD). Oral triple therapy, metformin + TZD + incretin-based drug, has several theoretical advantages but is not supported by any published trial. Finally, obtaining the acceptance of injections once to twice daily vs. oral administration of OADs will probably remain difficult during the first years of treatment in many patients. Nevertheless a long-acting release exenatide formulation (i.e. once weekly), for subcutaneous injection in patients with type 2 diabetes under development shows promising preliminary results. If confirmed, the use of this new class of drugs should be largely developed from monotherapy to combinations (bitherapy or tritherapy), and even instead of insulin or in association with insulin. The long-term effect of GLP-1 based agents on glycaemic control has not yet been established, and their potential impact on β-cell function in humans remains an area of active investigation. So, further studies are required and will allow progressively determining the use of incretin-based agents in T2DM treatment strategy. Their efficacy, safety and their cost vs. older strategies, will be really evaluated by physicians in the real daily practice and by large and long term systematic surveys, as recently shown in other therapeutic fields.

Résumé

Inhibiteurs du DPP-4 et analogues du GLP-1 : pour qui ? Quelle est la place des incrétines dans le traitement du diabète de type 2 ?

Cette revue tente de situer comment les nouvelles médications fondées sur l’effet incrétine (GLP-1), inhibiteurs des DPP-4 (sitagliptine, vildagliptine), et les analogues du GLP-1 (exénatide et liraglutide) dans les futures recommandations et donc la pratique courante pour traiter les diabétiques de type 2 (DT2). Les inhibiteurs des DPP-4 abaissent l’HbA1c de 0,5 à 1,1 %, sans hypoglycémiénie ni prise de poids. Les analogues du GLP-1 doivent être injectés mais montrent un abaissement plus marqué de l’HbA1c (0,8 à 1,7 %), une perte de poids (1,75-3,8 kg) mais plus d’effets secondaires et environ 10 à 20% d’interruption thérapeutique. Si l’on tient compte de l’efficacité, de la tolérance et du coût de ces médicaments, elles ne devraient pas remettre en cause l’usage de la metformine comme première ligne de traitement du DT2, sauf en cas d’intolérance absolue, contre-indication ou chez le sujet âgé. Nombreux sont les travaux qui montrent l’intérêt de la bithérapie associant metformine + inhibiteurs des DPP-4 plaissant pour cette stratégie comme une seconde ligne de traitement à privilégier, en particulier, si l’on considère les recommandations actuelles plus strictes donc exposant à un risque hypoglycémié qui plus élevé avec les sulfamides hypoglycémiéciants et la prise de poids sous TZD. La trithérapie metformine + TZD + incrétine, semble en théorie logique, mais aucune étude n’est disponible pour soutenir cette proposition. Pour les analogues du GLP-1 l’acceptation d’une ou deux injections par jour en réduit l’usage large. Toutefois les premières données obtenues avec l’exénatide d’action prolongée (une injection/semaine) ouvre une nouvelle perspective avec une acceptabilité beaucoup plus grande dès même la monothérapie, en bi- et trithérapie, voire à la place de certaines indications de passage sous insuline ou en association avec l’insuline. Les effets protecteurs montrés chez l’animal sur la cellule bêta-pancréatique doivent être confirmés par des études larges et de longue durée chez l’homme. De même, des études seront nécessaires.

© 2008 Elsevier Masson SAS. All rights reserved.
1. Introduction

New and more stringent international guidelines, ADA/EASD consensus statement, have been recently launched [1]. The French recommendations published few months later, are roughly similar with some nuances mainly considering the HbA1c threshold, 6.5% vs. 7%, for introducing metformin since the very beginning of the disease or for addition of medications and transition to new regimens [2].

New concepts and new drugs have been recently introduced. The ‘incretin effect’, refers to the amplification of the insulin response to glucose when delivered orally as opposed to intravenously. Incretin hormones are secreted from the gastrointestinal tract during food intake. Two peptides have been identified, the gastric inhibitory polypeptide (GIP), and the glucagon like peptide-1 (GLP-1), GLP-1 appearing as mainly responsible for the majority of the incretin effect on pancreatic β-cell function with therapeutic target. Moreover GLP-1 reduces basal and post-prandial glucagon secretion by α-cells, slows gastric emptying and exerts some favourable effects on appetite and saticity. Secretion of GLP-1 is lower than normal in patients with type 2 diabetes. Increasing GLP-1 improves glycaemia, which suggests that the hormone may contribute to the pathogenesis of the disease. Finally animal data have shown preservation or enhancement of β-cell function via β-cell proliferation, neogenesis and inhibition of apoptosis. This last effect should prevent the decline in B-cell function and the loss of insulin secretory capacity that is the fundamental cause of type 2 diabetes. The major therapeutic obstacle to using native GLP-1 is its very short half-life of 1-2 min following its secretion or exogenous administration, mainly due to the enzyme DPP-4. Thus, GLP-1 cannot be used as a practical treatment. For that reason, two current approaches have been developed to enhancing endogenous GLP-1 action in vivo: incretin mimetics resistant to DPP-4 such as GLP-1 analogues as exenatide or liraglutide, and the DPP-4 inhibitors which potentiate the endogenous incretin hormones [16]. A remarkable specificity is represented by the fact that the insulin secreting effect and the inhibition of glucagon by these drugs end when the glycaemia is normalized [3]. Thus they can sustain reductions in HbA1c to clinically meaningful levels with minimal or no hypoglycaemic events and no weight gain.

Thus this paper addresses the question: “Which place for incretins in the strategy of treatment of type 2 diabetic patients, for which patients?” and subsequently “Are new drugs able to reach some unachieved targets?” Admittedly numerous data have been produced to introduce these molecules on the market, however it is probably too early to fully answer these questions because we are few experienced in their use in the real life.

2. Unmet needs in the treatment of type 2 diabetic patients

Prior to any consideration regarding the place of new pharmaceutical tools it is reasonable to identify and to list the advantages and the limits of the previous drugs and strategies. Thus, even if it represents the universal and unquestionable current first line therapy of all guidelines, metformin does not address the first disorder causing type 2 diabetes, β-cell dysfunction. Furthermore the intestinal intolerance of metformin and its use in older and fragile diabetics commonly restricted its use. Moreover the UKPDS showed a progressive failure of insulin secretion and a need for protecting β-cells against decline and apoptosis. Traditional treatments for type 2 diabetes do not address the progressive decline in β-cell function and therefore, despite therapy patients continue to advance in their disease state. Only thiazolidinediones (TZDs) are supposed to be able to play such a role. Sulfonylureas, which effectively stimulate insulin secretion, may cause hypoglycaemic attacks particularly in patients with mild hyperglycaemia or older subjects by inappropriate insulin secretion (i.e. whatever the glycaemic levels). Except metformin, all the oral drugs, sulfonylureas and TZDs as insulin injections favour weight gain and/or stimulate appetite. Lastly, in addition, in type 2 diabetic patients, glucagon production by α-cell, which normally maintains hepatic glucose production during fasting periods, is not suppressed by meal ingestion. This increased glucagon secretion leads to inappropriate levels of hepatic glucose output in the post-prandial state and consequently to hyperglycaemia. In summary, pancreatic islet dysfunction (α- and β-cells) is a rational target for the treatment of type 2 diabetes. As type 2 diabetes is a progressive disease, intensification of therapy is normally required over time. All the traditional oral antidiabetic drugs (OADs) with complementary modes of action must be rapidly associated for controlling the deterioration of glycaemia. All current agents are generally effective in the short to medium term, traditional treatment algorithms often fail to address the progressive...
development of the disease. Thus after a monotherapy, usually with metformin, bitherapy associating metformin plus sulfonylureas or TZDs is usually recommended and finally in some patients triple therapy with the three classes of OADs can be used in type 2 diabetic patients who maintain a significant residual insulin secretion and an obvious insulin resistance. After that step, all the guidelines recommend starting insulin injection with maintenance of OADs, at least metformin if tolerated and not contraindicated. However many patients do not benefit of insulin treatment with weight gain, hypoglycaemia and/or failure of their glycaemic control.

3. Glycaemic effects and potential advantages of incretins

To these several drawbacks of the previous approaches one must consider the need for an intensification of therapy (OADs) at lower thresholds in the new recommendations, from 7% in the international guidelines and 6.5% in the French ones. Thus, such new strategies, if well followed, increase the risk of hypoglycaemic attacks in patients for whom these rules are strictly applied and particularly the older and more fragile.

Unfortunately few studies have yet evaluated the glycaemic effects, benefits and drawbacks of DPP-4 inhibitors and GLP-1 analogues in the “conditions” of the present guidelines (i.e. at about 6.5 to 7% HbA1c). As with all the previous OADs, incretins reduce HbA1c according to the basal value, more in higher initial glycated haemoglobin and more modestly in less hyperglycaemic patients. Extensive preclinical and clinical developments have been conducted with DPP-4 inhibitors. The DPP-4 inhibitor sitagliptin has been recently launched in the US and will be soon in the European markets, a second one, vildagliptin, has been approved by European Health authorities, and large clinical studies are ongoing with two others, alogliptin and saxagliptin. The DPP-4 inhibitors have been currently evaluated as monotherapy and as combination therapy with previous OADs in patients with type 2 diabetes. To date, about 11 000 patients have been enrolled in vildagliptin and sitagliptin phase 2 and 3 studies until for > 52 weeks in some of them. In monotherapy sitagliptin as vildagliptin reduce HbA1c by 0.5 to 1.5% regarding the baseline value. Compared to metformin, sulfonylureas and TZDs the HbA1c improvement is usually equivalent or, although not always significantly, lower to that of these comparators. As with metformin and TZDs, DPP-4 inhibitors do not induce hypoglycaemic attacks, as metformin but by contrast to TZDs, DPP-4 inhibitors are neutral for body weight with possibly less other adverse events. In combination with metformin DPP-4 inhibitors allows reducing HbA1c below 7% in many patients with a basal value about 8 to 8.5% as well or a few less than with the classical combination sulfonylureas + metformin. However these results are obtained without weight gain and hypoglycaemia by contrast to the other combination.

4. DPP 4 inhibitors or metformin as the first the line monotherapy?

In all the available trials, the glycaemic results obtained with metformin monotherapy are equal or a few better when compared to that of DPP-4 inhibitors using either sitagliptin or vildagliptin [3-12]. Thus in absence of metformin intolerance or contraindication they are no reason to modify our use of metformin as the first line monotherapy, including because of its low cost an aspect which must remain a major medical driving determinant for treating such a worldwide epidemic disease. Tomorrow, this attitude should be replaced because of the “postulated” long term B-cell protection with DPP-4 inhibitors which may modify the course of diabetes. However, this must be confirmed by long-term controlled studies to demonstrate sustained glycaemic control that translates into beta-cell preservation. However from now the use of DPP-4 inhibitors must be considered as a promising monotherapy in older type 2 diabetic patients and/or with kidney deficiency. In an oral communication, Pratley commented that the efficacy of DPP-4 inhibitors may be somewhat greater among individuals with BMI < 30kg/m2 and in older rather than younger individuals [13].

5. DPP 4 inhibitors as the first combination after metformin monotherapy failure?

By contrast, while the DPP-4 inhibitors do not lower glucose to a greater extent than existing therapies, they offer many potential advantages which could modify the second line of treatment in type 2 diabetic patients [15-18]. Combination of metformin with DPP-4 inhibitors mainly in moderately hyperglycaemic patients (6.5-7.5% HbA1c) should become the favourite second line treatment even in older and fragile patients. Actually, regarding the present HbA1c threshold for intensification of therapy after metformin monotherapy failure, this combination offers two advantages: no hypoglycaemia and no weight gain. Thus, this new association should represent the future first line combination of OADs. On the other hand, the combination metformin-DPP-4 inhibitors should be a better choice compared to metformin-TZDs combination regarding the less choice of two insulin sensitizing OADs a frequent body weight gain induced by TZDs and their restricted use in older patients. Nevertheless we must consider the strong and fast improvement of glycaemic control with the classical combinations metformin-sulfonylureas in type 2 patients exhibiting higher basal HbA1c values. It is possible after a longer use of the “new” vs. the “former” insulin secretors, that it comes to light that some patients remain better controlled with the older ones with few
undesirable side effects (mainly a mild weight gain) and at a lower cost. However, in patients not tolerating metformin, DPP-4 inhibitors combined with a TZD represents an interesting alternative. This has been recently shown by J. Rosenstock et al, using vildaglaptin 10 mg + pioglitazone 30 mg, with 65% of the patients below 7% HbA1c after 24 weeks treatment, thus providing a better glycemic control than each component monotherapy with minimal hypoglycaemia and the same weight gain and oedema when compared to pioglitazone alone [18]. Bitherapy DPP-4 inhibitor + metformin vs. DPP-4 inhibitor + TZD have not yet been yet compared for their ability for both efficacy, tolerability and durability of these possible combinations.

6. The TZDs mainly pushed back to the third line (i.e. triple therapy)?

According to the previous strategy, it fits into the same scheme to propose to add a TZD in patients inadequately controlled by a bitherapy “metformin-DPP-4 inhibitors from low HbA1c (≤7%) without hypoglycaemic risk. This should be proposed to some patients before initiating insulin treatment. Not only patients who refuse insulin but rather presenting clinical and biological characteristics, i.e. more likely prompt to have a durable benefit with a triple therapy compared to insulin or who failed under insulin treatment. However no study is available to support this “recommendation”. The combination of sulfonylureas and DPP-4 inhibitors appears as few relevant both in bitherapy and tritherapy with extremely modest HbA1c improvements [19]. Addition of DPP-4 inhibitors to insulin in type 2 diabetic patients poorly controlled with high dose of insulin has been studied in one recent trial with little benefit [20].

7. Which place for GLP-1 agonists?

Clinical trials involving GLP-1 agonists are less numerous than the ones with DPP-4 inhibitors [21-25]. Nevertheless it is possible to draw some lessons from their different mode of action, tolerance, side effects and from the data of these studies. As DPP-4 inhibition primarily supports the physiological functions of endogenous GLP-1 without reaching its physiologic level, GLP-1 agonists lead to pharmacological GLP-1 levels. Thus, hyperglycaemia is usually more reduced with GLP-1 agonists when compared to that obtained with DPP-4 inhibitors Clinical trials with the incretin mimetic exenatide (two subcutaneous injections per day) and liraglutide (one subcutaneous injection per day) show reductions in post-prandial glycaemia, HbA1c (-0.8% to -1.7%), associated with weight loss (1.75 kg - 3.8 kg). The similar glucose control obtained with a fixed-dose exenatide and insulin glargine in patients with long-standing type 2 diabetes that was inadequately controlled by metformin or a sulfonylurea is questionable [26]. Actually the glargine titration used in this trial and the final insulin doses achieved seem to be much lower to that previously used and recommended.

Finally obtaining the acceptance of injections once to twice daily vs. oral administration of OADs will probably remain difficult during the first years of treatment in many patients. Nevertheless a long-acting release (LAR) exenatide formulation (i.e. once weekly), for subcutaneous injection in patients with type 2 diabetes, is under development with promising preliminary results [27]. Whether these first data are confirmed, the use of this new class of drugs should be largely developed from monotherapy to combinations (bitherapy or tritherapy) and even instead of insulin or in association with insulin. The most common adverse events associated with GLP-1 receptor agonists are gastrointestinal symptoms, which lessen over time, but contribute to a substantial, about 10-20%, treatment interruption [26].

8. Conclusion

It appears likely that early and aggressive treatment with multiple drug combinations will become more common in the management of T2DM. Progressive loss of β-cell function and mass makes it difficult for patients to maintain glycaemic control. The two strategies for GLP-1 based therapy are both promising novel treatments of type 2 diabetes. These latest pharmacological agents designed to combat beta-cell dysfunction include the GLP-1 (e.g. exenatide) analogue and the DPP-4 inhibitors (e.g. sitagliptin and vildagliptin). Obesity and hypoglycaemic risk are two major drivers of the type 2 diabetes condition, and agents that improve weight loss in overweight or obese type 2 patients without hypoglycaemia represent a real progress. DPP-4 inhibitors are orally active, safe, and highly tolerable, with few or no risk for hypoglycaemic attacks. Furthermore, they show sustained and clinically significant improvement in glycaemia in both monotherapy and combination with metformin and thiazolidinediones, and they are body weight neutral. The long-term consequences of DPP-4 inhibition on β-cell function and the durability of glucose lowering achieved with sustained DPP-4 inhibition require careful clinical assessment. The new treatment modalities discussed here offer hope for improved outcomes and for meeting the considerable public health challenges posed by this complex condition. GLP-1 analogues show sustained and more clinically significant improvement in glycaemia in both monotherapy and combination with metformin and thiazolidinediones, and they reduced body weight. However they are injected once or two times a day. DPP-4 inhibitors are better tolerated and are oral rather than injected, suggesting a particular role in early treatment and, perhaps, as in prevention of diabetes. Nevertheless, the long-acting release (LAR) exenatide formulation (i.e. once weekly) may change the acceptance of injections for an early use in a majority of type 2 diabetic patients. Moreover, facing this increase in the number of drugs for
treating type 2 diabetes and their multiple possible combinations, it will become more complicated for the physicians to determine which treatment is the better for a given patient. Studies ensuring the phenotype determination (clinical and biological) of good responders to each drug family and combination, should help the experts for the future recommendations and the physicians for avoiding accumulation or successive uses of therapy at family drugs instead of continuously the other components of treatment failures. Lastly regarding the epidemic of type 2 diabetes worldwide we must consider the cost of the different treatment, particularly when considering the need for multiple combination and long term duration of the treatment.

Conflicts of interest: S. Halimi: Clinical trials as co-investigator or study contributor (MSD); Occasional involvements: expert reports, advisory services (Novartis); Conferences: attendance as contributor (MSD, Novartis), attendance as audience member: cost of travel and accommodation paid for by an organisation or company(MSD).

References