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Review Article

Would other oral hypoglycaemics persist as an adequate 1ST line add-on therapy to metformin in patients with type 2 diabetes mellitus? No, it's time to refocus!

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ABSTRACT

Adequate glycemic control in type 2 diabetes remains a difficult but achievable goal. The development of new classes of glucose-lowering medications, including in particular the incretin-based therapies, provides an opportunity to utilize combinations of medications which target multiple physiologic abnormalities in type 2 diabetes. Complementary combination therapy with sitagliptin–metformin lowers glucose via enhancement of insulin secretion, suppression of glucagon secretion, and insulin sensitization. Use of this combination in diabetes management will provide a greater degree of glycosylated hemoglobin-lowering than that seen with the use of either drug as monotherapy, is unlikely to cause significant hypoglycemia, and is generally associated with weight loss. The effectiveness, tolerability, and potential cost savings associated with the use of sitagliptin–metformin combination therapy make this an attractive option in diabetes management. The possible beneficial effects of this therapy on beta cell function, as well as its cardiovascular impact, remain inadequately explored but are of significant interest.

Key Words; Sitagliptin, Type 2 diabetes mellitus, Incretin hormone, GLP -1, GIP, Add on to metformin.

INTRODUCTION

Current perspective on treatment of type 2 diabetes: Because the number of individuals affected by diabetes is continuing to increase worldwide, the need for effective management assumes ever greater urgency. In 2007, it was estimated that 7.8% of the US population was affected by diabetes, with the global number of affected individuals likely to exceed 220 million.[1,2] Although glycemic control has been shown to minimize the development and progression of diabetes-related complications, it remains elusive for many.[3] The National Health and Nutrition Examination Survey 2003–2004 found that only 57.1% of patients with diabetes had a glycosylated hemoglobin (HbA1C) level below the current treatment target of 7.0%.[4] Despite the improvement from 35.8% at HbA1C goal in the 1999–2000 survey, almost half of individuals with type 2 diabetes remain suboptimally managed. The challenges encountered in the achievement and maintenance of adequate glycemia are many, due in large part to the complex pathophysiology which contributes to the development of type 2 diabetes. Metabolic abnormalities including insulin resistance, at least relative insulin deficiency, and glucagon excess must be considered when prescribing effective glucose-lowering therapies.
Recommendations regarding the institution and intensification of antihyperglycemic therapy have become more aggressive in recent years. Reliance on lifestyle modification alone has been discouraged, because this approach has not been found likely to accomplish either adequate or durable glycemic control for most.[5]

Initiation of glucose-lowering medication at the time of diabetes diagnosis, generally in the form of metformin, has been suggested.[5] Although this may improve glycemic control early on in the course of the condition, many traditionally used glucose-lowering medications (including metformin) have not been found to alter substantially the progressive deterioration in beta cell function and glycemia that occurs in type 2

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diabetes.[6] Non-adherence to prescribed therapies, often due to cost, inconvenience, medication side effects, and/or regimen complexity, may also present a challenge to glycemic control. Furthermore, diabetes care providers may fail to implement effective therapies due simply to clinical inertia or perhaps a poor understanding of the expected potency or durability of the glucose-lowering therapies that they prescribe. On a more positive note, the variety of antihyperglycemic medications now available may permit greater individualization of therapy, and perhaps more successful therapy, than had previously been possible. Newer classes of medications, particularly those which work via the incretin pathway, achieve glucose lowering without the risk of weight gain or hypoglycemia conveyed by more traditional therapies, such as insulin or sulfonylureas. Because many agents with differing mechanisms of action are now available, complementary combinations of these medications may permit glucose lowering in an effective and well tolerated fashion. Several studies have demonstrated that combinations of different classes of oral agents are more effective in glucose lowering than are maximal doses of a single drug, leading to recommendations by many authors that combination therapies be considered early or initially in the management of type 2 diabetes.[7–10] For example, the American Association of Clinical Endocrinologists suggests initial combination therapy for patients with an HbA1C in the range of 7%–8% at the time of diabetes diagnosis.[11] In addition to targeting multiple metabolic abnormalities underlying type 2 diabetes, combination therapies may result in improved adherence due to the smaller number of pills needed to be taken daily, and in some cases a reduction in overall medication costs.

Furthermore, combinations of less than maximal doses of medications may permit effective glucose lowering with a minimization of the side effects associated with each individual drug class. Ideally, combination therapies should be well tolerated, convenient to take, have few contraindications, have a low risk of hypoglycemia and weight gain, and be reasonably effective over both the short and long term.

Hyperglycemia is a key factor underlying complications of type 2 diabetes, and, therefore, reducing hyperglycemia is a critical aim of treatment of the disease. Improving hyperglycemia has thus been shown to reduce the risk of microvascular complications and may also reduce macrovascular complications.[12,13] The basis for treatment is lifestyle changes with increased physical activity and dietary modifications. If these treatments are not sufficient, pharmacological treatment with metformin is recommended.[14] However, due to the progressive nature of the disease, additional pharmacological treatment is often required. Several options exist: sulfonylureas, thiazolidinediones, meglitinides, α-glucosidase inhibitors and insulin.[14,15] There are, however, limitations with these pharmacological treatments, such that even with aggressive treatment using these approaches, glycemic control often deteriorates. Furthermore, current therapy is often associated with adverse events. These adverse events include hypoglycemia with sulfonylureas and insulin, gastrointestinal discomfort with biguanides (such as metformin), and increased body weight, edema and cardiac insufficiency with thiazolidinediones.[16–19] Furthermore, the current therapies do not target all pathophysiological aspects of type 2 diabetes. Thus, dysregulation of glucose metabolism in type 2 diabetes is caused by a combination of insulin resistance, impaired insulin secretion, augmented glucagon secretion and reduced β-cell mass.[10–23],Whereas insulin resistance is treated by biguanides and thiazolidinediones, and insulin secretion is treated by sulfonylureas, no therapy treats the hypersecretion of glucagon and the reduced β-cell mass. There are thus several unmet needs in the treatment of diabetes which urge the development of novel treatment. Recently, several new approaches have emerged to meet these challenges. These novel therapies include the amylin analog pramlintide and the GLP-1 receptor agonists, including exenatide and liraglutide. [24–26] Another novel class of compounds is inhibitors of the enzyme dipeptidyl peptidase- 4 (DPP-4). The DPP-4 inhibitors, which prevent the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), increase the endogenous concentrations of these hormones which prolongs their actions and improves glycemia. [27–31]Several DPP-4 inhibitors have been developed and are in various stages of clinical development. Sitagliptin, vildagliptin and saxagliptin are approved for use in several countries.[31]

Physiology of incretin hormones and the incretin effect: Incretins are a group of insulinotropic hormones that are secreted by the gut in response to food intake. The class of hormones was first discovered in 1902, and in 1964 the incretin effect was described. [32-34] The incretin effect refers to the more robust increase in insulin secretion in response to orally ingested glucose, as compared to the response elicited by glucose given intravenously. In the seminal trials, this effect was maintained despite the presence of higher blood glucose levels during the intravenous infusion. [33, 34] Subsequently, more details have emerged about

the two hormones largely responsible for the incretin effect: glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is the most potent known incretin. The level of GLP-1 rises quickly in response to food ingestion; this has direct effects on pancreatic endocrine function, including both insulin release from the beta cells and suppression of glucagon release from the alpha cells. There is some limited evidence that GLP-1 also acts at peripheral tissues to improve insulin utilization.[35] Other effects of GLP-1 include slowed gastric emptying and the promotion of satiety at the level of the central nervous system.[36] GIP, the other well-described but perhaps less well understood incretin hormone, promotes similar food and glucose-dependent insulin release. However as opposed to GLP-1, it may exert a stimulatory effect on glucagon release.[37] An important feature of both incretin hormones is that their activity is glucose-dependent: glucose lowering activity ceases when blood glucose levels fall below 65 mg/dL.[38] Furthermore, in animal models, both GLP-1 and GIP are suspected to have a stimulatory effect upon the growth, proliferation, and differentiation of beta cells.[36] The half-lives of GLP-1 and GIP are only a few minutes long, as they are rapidly degraded to largely inactive metabolites by DPP-4. [38]

Incretin hormones and DPP-4 in type 2 diabetes

In individuals with type 2 diabetes, the incretin effect appears to be blunted. [39] This blunting has been attributed to 2 factors: GLP-1 levels are lower and GIP exerts a lesser physiologic effect than seen in normoglycemic individuals. Responsiveness to GLP-1 is generally preserved; infusion of GLP-1 to individuals with diabetes has been shown to lower both postprandial and fasting blood glucose levels. [38,40] Conversely, there appear to be relatively normal levels of GIP in persons with type 2 diabetes, but their physiologic response to GIP is diminished [41] Whether or not abnormalities in DPP-4 levels or degradative activity exist in patients with diabetes is still unclear.

The administration of DPP-4 inhibitors to individuals with type 2 diabetes has been shown to raise levels of endogenous GLP-1 and GIP, which in turn results in a glucose-appropriate increase in insulin secretion and suppression of glucagon release.[42] In patients with type 2 diabetes, administration of DPP-4 inhibitors has been shown to improve markers of insulin processing, including homeostasis model assessment of beta cell function (HOMA-β) and the proinsulin:insulin ratio.[43] Furthermore, there are animal data to suggest that pancreatic beta cell mass may be preserved; beta cells may even be stimulated to grow and proliferate in the presence of these agents. [44] However, no comparable anatomic data in humans are available.

MECHANISMS OF ACTION AND PHARMACOLOGY

Sitagliptin: Sitagliptin is an orally administered agent which exerts its glucose-lowering effects via inhibition of the activity of the DPP-4 enzyme. This enzyme, in addition to circulating in a soluble form in plasma, is expressed in a variety of tissues including the liver, kidney, lung, and lymphocytes. [27] DPP-4 is responsible for the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucosedependent insulinotropic peptide (GIP), which are released from the gut in response to food intake. The active intact forms of GLP-1 and GIP both stimulate insulin secretion in a glucose-dependent fashion; additionally, GLP-1 contributes to glucose homeostasis via regulation of gastric emptying andglucose-dependent suppression of glucagon secretion.[13] Individuals with type 2 diabetes are deficient in GLP-1 and have diminished responsiveness to GIP.[38-40] Sitagliptin therapy in individuals with type 2 diabetes increases levels of and prolongs the half-lives of the active intact incretin hormones; these, in turn, lower glucose via enhancement of the insulin response to glucose and a decrease in glucagon secretion.[30]

The likelihood of hypoglycemia due to DPP-4 inhibitor monotherapy is low because the incretin hormones do not exert glucose-lowering effects when glucose levels are below normal.

Sitagliptin is available in an oral tablet which may be administered with or without food. It is highly selective for DPP-4, with significantly greater affinity for that enzyme than for the related enzymes DPP-8 and DPP-9. [45]

Administration of sitagliptin rapidly inhibits the activity of DPP-4 in a dose-dependent fashion. Doses of 50 mg and 100 mg inhibit the activity of the enzyme by 80% over 12 and 24 hours, respectively. This degree of inhibition yields a two- to three-fold increase in active GLP-1 levels, and is the level of inhibition at which near maximal glucose lowering is seen. In individuals with type 2 diabetes, sitagliptin therapy exerts its glucose-lowering effects via increased insulin secretion and suppression of glucagon release. The majority of the administered drug is excreted unchanged in the urine via active tubular secretion. [45,46] Sitagliptin is minimally metabolized prior to excretion and does not appear to inhibit or induce cytochrome P450 enzymes, making the potential for adverse interactions with other medications

low. No significant alterations in the pharmacokinetics of rosiglitazone, glyburide, or metformin are known to occur following sitagliptin administration. [45, 46] The usual recommended daily dose of sitagliptin is 100 mg; however, because renal insufficiency increases drug exposure, the dose should be reduced in individuals with modest or severe renal dysfunction. The recommended daily dose is 50 mg for patients with a creatinine clearance 30–50 mL/min and 25 mg daily for patients with a creatinine clearance , 30 mL/min. Renal function should be monitored periodically in patients using sitagliptin in order to ensure appropriate medication dosing.[47]

SAFETY AND TOLERABILITY

Side effects: There have been numerous individual trials and 3 large meta-analyses to examine the safety and tolerability of the DPP-4 inhibitors as a class. [48,49,50] The analyses have shown that these medications are generally well-tolerated in the short term. With respect to hypoglycemia, the DPP-4 inhibitors have performed well. Their use has not been commonly associated with any degree of hypoglycemia. Although a few individual trials have found an increase in mild hypoglycemia when DPP-4 inhibitors are combined with other antidiabetic medications. [51,45,52,53]. 2 meta-analyses have shown that there has been no significant difference from placebo, even when DPP-4 inhibitors are combined with sulfonylureas or insulin. [50,54]

Monami et al examined unpublished data and described five cases of severe hypoglycemia in sitagliptin monotherapy; these cases were fewer than those in sulfonylurea comparator groups and were not discussed in the published literature.50 Another feature in favor of the use of DPP-4 medications is that they have not been associated with weight gain. Metaanalyses of sitagliptin, vildagliptin, alogliptin, and saxagliptin concluded that there has been no clinically significant effect on BMI in placebo-controlled trials.[50]

Reported side effects have generally been mild, such as increased rate of headaches with vildagliptin and increased rates of upper respiratory tract infections with sitagliptin.[50] Increased rates of other mild infections, such as urinary tract infection, have been reported in individual trials and were associated with use of sitagliptin in a 2009 Cochrane review.[54] However, a more recent meta-analysis did not confirm this association.[50] In the postmarketing period, the use of sitagliptin has been associated with cases of mild to severe hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin conditions. These have occurred in the first few months of therapy; in one case, after the first dose. Continued use of or re-exposure to sitagliptin is contraindicated in patients who have experienced hypersensitivity reactions.[55] Vildagliptin has been associated with rare cases of hepatic dysfunction, and should not be used in patients with pre-existing moderate to severe hepatic failure.[56] Vildagliptin was also associated with a skin blistering condition in nonclinical toxicology studies with primates. This has not been reported in human studies at recommended therapeutic dosages, and is not reported in post-marketing data. [57] More studies are needed to examine the potential immunomodulatory effects of vildagliptin and determine whether they are greater than that seen with use of other agents in this class. The US Food and Drug Administration (FDA) recently called attention to a number of cases of acute pancreatitis, which were temporally associated with the initiation of sitagliptin.[58] This announcement raises concern given that a similar association had been observed with the GLP-1 agonist exenatide.[59] The classes of drugs that utilize the incretin pathway are known to have direct effects on the structure of the pancreas in rodent models, suggesting the possibility for a causal relationship with pancreatitis, although the mechanism is unclear. In one rodent study, use of GLP-1 receptor agonists was associated with increase in pancreatitis-associated gene expression but not with pancreatitis. [60] Matveyenko et al conducted a rodent model study to examine the effects on the pancreas of metformin and sitagliptin in combination. The two drugs appeared to have synergistic effect to preserve beta-cell mass and function, but use of sitagliptin was associated with increased pancreatic ductal turnover, ductal metaplasia, and, in one rat, pancreatitis. [61] These findings do raise concern; however, this information has yet to be confirmed in humans.

Human data exist in the form of a retrospective analysis of around 88,000 patient hospitalization records, which examined rates of admission for acute pancreatitis in patients using incretin-based therapies (exenatide and sitagliptin) compared to matched groups of patients using metformin and glyburide. They found that hospitalizations for acute pancreatitis within 1 year of initiation of the respective drugs were similar for the four medications, with a rate of 0.13% per year of patients on exenatide and 0.12% per year for patients on sitagliptin. [62] Given that the human data at this point are limited to postmarketing reports and retrospective data analysis, the true relationship of pancreatitis to incretin-based therapy remains unknown. Given the baseline rate of pancreatitis in people with diabetes, it is

currently difficult to know if reports of pancreatitis in people on incretin therapies are truly attributable to drug usage. Data accumulated from large, long-term trials with sitagliptin and other DPP-4 inhibitors may provide much needed information regarding this relationship. For now, the FDA recommends that physicians warn patients about the potential risk as well as the symptoms of pancreatitis, and discontinue the drugs if symptoms or signs of pancreatitis develop. [58]

The FDA now requires that therapies approved to treat type 2 diabetes should provide data to demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.[63] Saxagliptin was the first drug approved following establishment of this guideline; its use was not associated with an increased risk of cardiovascular events in pooled data from eight pre-marketing clinical trials.64 However, the number of cardiovascular events occurring during these trials was inadequate to confidently exclude a differential effect; thus a long-term cardiovascular outcomes trial of this medication will be required. Although analysis of data from early studies of sitagliptin and vildagliptin found that mortality and cardiovascular event rates were similar between these drugs and comparators, no individual trial with these agents was powered to examine this outcome.50 A long-term cardiovascular outcomes trial of sitagliptin therapy in individuals at high risk for such complications began enrollment in December of 2008. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) is an international trial of 14,000 individuals with diabetes and cardiovascular disease which will assess the impact of sitagliptin therapy on events including cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. [64]

RATIONALE FOR USE OF A SITAGLIPTIN–METFORMIN COMBINATION

As outlined in the preceding sections, the differing mechanisms of action of sitagliptin and metformin would be expected to have additive effects upon glucose lowering in type 2 diabetes. The three main defects in diabetes, which include impaired insulin secretion, insulin resistance, and glucagon excess, will all be targeted by such a combination of medications. Although both metformin and sitagliptin monotherapy have been found to increase GLP-1 levels, this appears to occur through different physiologic pathways. Indeed, coadministration of sitagliptin–metformin to individuals with type 2 diabetes has been found to result in GLP-1 elevation in excess of that seen with administration of either drug alone.65 The complementary mechanisms of action, lack of adverse pharmacologic interactions, and limited potential for hypoglycemia associated with the two medications make this an attractive therapeutic combination. Fixed combination tablets are available in doses of 50 mg sitagliptin 500 mg metformin or 50 mg sitagliptin 1000 mg metformin. [65]

CONCLUSION

Therapy for type 2 diabetes is complex; many patients require multiple medications to reach optimal glycemic targets. As outlined in the ADA/EASD algorithm for diabetes medications, there are multiple potential combinations of medications for any individual; the provider must consider co-morbidities and patient preferences when making these decisions. Although the DPP-4 inhibitor class is not yet well-studied enough to have been included in the algorithm, studies suggest that these drugs' mechanisms of action complement those of traditionally used diabetes medications. The DPP-4 inhibitors have been criticized for having lower glucose lowering efficacy than other available therapies, particularly insulin. [4] However, the active comparator trials data suggest that they can be as effective as more traditionally prescribed therapies. Furthermore, they are generally well tolerated, do not cause weight gain, and may provide some beta cell protection.

Unlike many traditional medications, these drugs rarely cause hypoglycemia and some agents have no major contraindications to use. These attributes make this class of drugs attractive for information use in the elderly, for those who have multiple co-morbidities precluding the use of other medications, and for those in whom insulin therapy proves difficult. Data on these drugs continue to be accrued, and it is likely that the safety concerns related to the immune system and pancreatitis will be prospectively and more comprehensively addressed. Long-term trials are also needed to determine if preliminary data suggesting beta cell preservation will be borne out in clinical practice. Further investigations are also needed to examine long-term effects of these agents on cardiovascular outcomes and mortality.

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