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What role will ‘gliptins’ play in glycemic control?

■ ABSTRACT

The gliptins, a new class of oral drugs for type 2 diabetes mellitus, lower blood glucose levels by a novel mechanism: ie, by inhibiting the enzyme dipeptidyl peptidase 4, thereby increasing the circulating levels of incretins (gut hormones that can boost insulin levels). This article reviews the current evidence on the effectiveness of gliptins and suggests several ways in which these agents could be used in diabetes treatment.

■ KEY POINTS

Sitagliptin (Januvia) is now available, and vildagliptin (Galvus) is awaiting approval. Other gliptins are under development.

The gliptins effectively lower blood glucose levels, do not require titration, are unlikely to cause hypoglycemia, do not cause weight gain or loss, and are well tolerated.

Gliptins can be used alone or in combination with metformin (Glucophage) or a thiazolidinedione. Preliminary studies also show evidence of benefit when they are used in combination with insulin.

Comparative studies suggest that gliptins lower blood glucose levels by about the same amount as other oral hypoglycemic agents.

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THE “GLIPTINS”—THE NICKNAME FOR dipeptidyl peptidase 4 (DPP-4) inhibitors—are one of the newest classes of drugs for the treatment of type 2 diabetes mellitus.

These drugs work by prolonging the action of gut hormones called incretins, which boost insulin levels. The greatest advantage of the gliptins appears to be their ability to stimulate insulin production with little risk of corresponding hypoglycemia.

Sitagliptin (Januvia), the first commercially available DPP-4 inhibitor, has been approved by the US Food and Drug Administration (FDA) and is currently in clinical use, and vildagliptin (Galvus) awaits FDA approval at the time of this writing. Other drugs of this class are in development.

However, because these drugs are so new, a number of questions remain about their use. In this article, we discuss the rationale behind gliptin drugs, the evidence to date on their use alone or in combination with current oral hypoglycemic drugs (and even with insulin), and when and how to use them in daily practice.

■ THE NEED FOR MORE EFFECTIVE DIABETES TREATMENT

As the number of patients with type 2 diabetes continues its steep and steady rise,^{1,2} much work has gone into studying treatment goals and how to achieve them. Although experts generally agree on glycemic goals,³ we currently fail to achieve those goals in close to two-thirds of patients: only 37% have a hemoglobin A_{1c} (HbA_{1c}) value at or below the goal of 7%, and the same number have levels exceeding 8%.⁴

Part of the problem is that treatment regimens are not adjusted in a timely fashion. In a prescribing database of almost 4,000 patients with type 2 diabetes,⁵ the mean time from the first HbA_{1c} reading above 8% to an actual change in therapy was about 15 months for those taking metformin (Glucophage) alone, and 21 months for those taking a sulfonylurea alone. Another part of the problem is that, on average, patients with an HbA_{1c} of 8.0% to 8.9% can expect only a 0.6% lowering with the addition of one agent.⁶ Clearly, we need new pharmacologic approaches and new management paradigms. One new approach is the use of gliptins.

■ HOW GLIPTINS WORK

Incretins promote insulin secretion

We have known for more than 20 years that insulin levels rise considerably higher in response to an oral glucose load than to an intravenous glucose infusion, even though the plasma glucose concentrations may be similar.⁷ This phenomenon involves a myriad of neural and nutritional factors, but the gut hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) appear to be key.

These peptides—called incretins—have a high degree of homology, and both promote insulin secretion. However, GLP-1, produced by the L cells of the ileum and colon, inhibits glucagon secretion and slows gastric emptying, whereas GIP, secreted from the K cells of the duodenum, has no effect on glucagon and little effect on gastric emptying. Both peptides appear to promote pancreatic beta cell growth and survival,^{8,9} an effect that in theory might allow us to slow the progressive loss of insulin secretory capacity in type 2 diabetes.

Furthermore, the effect of GLP-1 on insulin secretion depends on the plasma glucose concentration, with a greater insulin secretory effect at higher glucose levels and minimal effect at euglycemic levels.¹⁰ This phenomenon suggests that drugs that boost GLP-1 activity should not cause the troublesome hypoglycemia typically seen in patients taking insulin, insulin secretagogues, sulfonylureas, or the meglitinides repaglinide (Prandin) or nateglinide (Starlix). Studies of

combination treatment with metformin and the GLP-1 receptor agonist exenatide (Byetta) have shown little risk of hypoglycemia,¹¹ offering evidence favoring this conjecture.

Inhibition of DPP-4 boosts incretin action

The challenge for creating treatments that take advantage of the beneficial effects of GLP-1 and GIP is that they have very short physiologic half-lives, ie, less than 10 minutes. GLP-1 and GIP both have two N-terminal amino acids that are quickly cleaved by DPP-4,¹² an enzyme present in the circulation¹³ and on endothelial cells.¹⁴

Currently, there are two classes of drugs based on incretins. One class, the incretin mimetics or GLP-1 receptor agonists, includes drugs that mimic the effect of GLP-1 but are not so quickly degraded by DPP-4. Examples of these drugs are exenatide, which is currently FDA-approved, and liraglutide, which is not yet approved.

On the other hand, by inhibiting the cleaving action of DPP-4, the gliptins can prolong the half-life of endogenous GLP-1, increasing its physiologic effects.

Studies comparing gliptins with GLP-1 receptor agonists are only at the preclinical phase. Liraglutide showed an antiglycemic effect similar to that of vildagliptin in an animal model of glucose intolerance.¹⁵ This and other^{16,17} preclinical studies have shown evidence of improved beta cell growth and survival with DPP-4 inhibitor treatment, to an extent similar to that reported with thiazolidinediones, whereas sulfonylureas show no evidence either of increase in beta cells or of improved intrinsic beta cell secretory function in these models. Of course, animal studies can only be cautiously extrapolated to potential effects in humans, and it is uncertain whether such benefits will occur with the therapeutic use of DPP-4 inhibitors.

■ RANDOMIZED CLINICAL TRIALS OF SITAGLIPTIN

Sitagliptin and vildagliptin have undergone a large number of studies in patients with type 2 diabetes. Several dosing regimens were tested, but we will restrict this discussion to studies that used 100 mg once a day or 50 mg twice a day. Of

Sitagliptin is effective alone, or with metformin or a thiazolidinedione

TABLE 1

Clinical trials of sitagliptin

INVESTIGATORS	DURATION	TREATMENT	NO. OF PATIENTS	HEMOGLOBIN A _{1c}	
				BASELINE	END
Aschner et al ¹⁹	24 weeks	Sitagliptin ^a	229	8.0%	7.4%
		Placebo	244	8.0%	8.2%
Raz et al ²⁰	18 weeks	Sitagliptin	193	8.0%	7.6%
		Placebo	103	8.1%	8.2%
Brazg et al ²¹ (crossover study)	4 weeks	Sitagliptin ^b + metformin ^c	13	7.7%	Not available
		Placebo + metformin	15	7.7%	Not available
Charbonnel et al ²²	24 weeks	Sitagliptin + metformin	453	8.0%	7.3%
		Placebo + metformin	224	8.0%	8.0%
Rosenstock et al ²³	24 weeks	Sitagliptin + pioglitazone	175	8.1%	7.2%
		Placebo + pioglitazone	178	8.0%	7.8%
Scott et al ²⁴	12 weeks	Sitagliptin ^b	112	7.8%	7.3%
		Glipizide ^d	123	7.9%	7.1%
		Placebo	125	7.9%	8.1%
Nauck et al ²⁵	52 weeks	Sitagliptin + metformin	588	7.5%	6.8%
		Glipizide + metformin	584	7.5%	6.8%

^a Sitagliptin (Januvia) dosages were 100 mg once a day, except where marked otherwise

^b 50 mg twice a day

^c All metformin (Glucophage) dosages were \geq 1,500 mg/day

^d Pioglitazone (Actos) dosages were 30 or 45 mg/day

^e Glipizide (Glucotrol) dosages were 5–20 mg/day

note, the effect of 50 mg twice daily may somewhat exceed that of 100 mg once daily,¹⁸ so these studies should be interpreted with caution. TABLE 1 summarizes the effect of sitagliptin on HbA_{1c} values in these studies.^{19–25}

Sitagliptin is effective when used by itself, reducing a baseline HbA_{1c} level of about 8% by 0.6% to 0.8%,^{19,20,24} and is similarly effective when combined with metformin^{21,22,25} or pioglitazone (Actos, a thiazolidinedione).²³ It also decreases fasting blood glucose levels and improves other measures of glucose control.

A study comparing sitagliptin and the sulfonylurea glipizide (Glucotrol) showed identical glucose-lowering over a 1-year period, with less hypoglycemia and weight gain with sitagliptin.²⁵ Hypoglycemic episodes occurred in 32% of patients taking glipizide but in only 5% of those taking sitagliptin.

Studies noted several trends in laboratory values, though none was associated with clinical evidence of adverse outcome:

- White blood cell counts were noted to increase in three of the studies by 4.7% to 10%, owing to increases in neutrophils^{19,20,22}
- Alkaline phosphatase concentrations decreased in four studies^{19,20,22,23}
- Uric acid levels increased in four studies.^{19,20,22,23}

RENAL INSUFFICIENCY SLOWS SITAGLIPTIN CLEARANCE

Lower doses and periodic monitoring of renal function are recommended in patients taking sitagliptin who have some degree of renal insufficiency. Clearance of sitagliptin is delayed in patients with renal insufficiency (creatinine clearance < 50 mL/minute).

In a placebo-controlled study of sitagliptin safety, Scott et al²⁶ found that the area under the sitagliptin concentration-time curve was 2.3 times greater in patients with moderate renal

TABLE 2

Clinical trials of vildagliptin

INVESTIGATORS	DURATION	TREATMENT	NO. OF PATIENTS	HEMOGLOBIN A _{1c}	
				BASELINE	END
Ristic et al ²⁸	12 weeks	Vildagliptin ^a	63	7.6%	7.1%
		Placebo	58	7.8%	7.7%
Dejager et al ²⁹	24 weeks	Vildagliptin	92	8.4%	7.2%
		Placebo	94	8.4%	8.1%
Ahrén et al ³⁰	12 weeks	Vildagliptin + metformin ^b	56	7.7%	7.1%
		Placebo + metformin	51	7.8%	7.9%
	52 weeks	Vildagliptin + metformin	42	7.6%	7.1%
		Placebo + metformin	29	7.8%	8.2%
Bosi et al ³¹	24 weeks	Vildagliptin + metformin ^c	185	8.4%	7.5%
		Placebo + metformin	182	8.3%	8.5%
Garber et al ³²	24 weeks	Vildagliptin + pioglitazone ^d	136	8.7%	7.5%
		Placebo + pioglitazone	138	8.7%	8.1%
Fonseca et al ³³	24 weeks	Vildagliptin ^e + insulin	144	8.4%	7.9%
		Placebo + insulin	152	8.3%	8.2%
Dejager et al ³⁴	52 weeks	Vildagliptin	526	8.7%	7.7%
		Metformin ^f	254	8.7%	7.3%
Rosenstock et al ³⁵	24 weeks	Vildagliptin	459	8.7%	7.6%
		Rosiglitazone ^g	238	8.7%	7.4%
Rosenstock et al ³⁶	24 weeks	Vildagliptin	154	8.7%	7.6%
		Pioglitazone ^h	161	8.7%	7.3%
		Vildagliptin + pioglitazone	148	8.7%	6.8%

^a Dosages of vildagliptin (Galvus) were 100 mg once a day, unless otherwise indicated

^b Vildagliptin 50 mg once a day plus metformin (Glucophage) 1,500–3,000 mg/day

^c ≥ 1,500 mg/day

^d Pioglitazone (Actos) 45 mg daily

^e 50 mg twice a day

^f 2,000 mg/day

^g Rosiglitazone (Avandia) 8 mg/day

^h 30 mg/day

insufficiency (creatinine clearance rate 30–49.9 mL/minute), 3.8 times greater in those with severe renal insufficiency (15–29.9 mL/minute), and 4.5 times greater in those with end-stage renal disease (< 15 mL/minute).

The Januvia package insert²⁷ recommends that the daily dose be decreased to 50 mg in patients with creatinine clearance rates of 30 to 49.9 mL/minute (serum creatinine > 1.7 mg/dL in men, > 1.5 mg/dL in women), and that the dose be decreased to 25 mg per day in those with creatinine clearance rates below 30 mL/minute (creatinine > 3.0/2.5 mg/dL).

CLINICAL TRIALS OF VILDAGLIPTIN BEGIN

Vildagliptin has also undergone extensive clinical testing (TABLE 2).^{28–36} The trials to date indicate that it is effective when used alone, reducing HbA_{1c} levels by 0.5% to 0.9% from a baseline of 8%.^{28,29,34–36} The effect appears to be similar when vildagliptin is used in combination with metformin^{30,31} or pioglitazone.^{32,36}

A study comparing vildagliptin against metformin³⁴ showed less glucose-lowering over a 1-year period with vildagliptin, albeit

with fewer gastrointestinal side effects, while comparisons with rosiglitazone (Avandia)³⁵ and with pioglitazone³⁶ showed similar glucose-lowering ability.

In a 24-week study,³³ 256 patients with type 2 diabetes who had a mean body mass index of 33 kg/m² and who were taking more than 30 units of insulin daily (an average of 82 units) were randomized to additionally receive either vildagliptin 50 mg twice daily or placebo. The HbA_{1c} decreased by 0.5% with vildagliptin and by 0.2% with placebo, from a baseline level of 8.5%. Of interest, 33 patients receiving vildagliptin had a hypoglycemic episode (a total of 113 events), compared with 45 patients in the placebo group (185 events). None of the episodes in the vildagliptin group was classified as severe, whereas six episodes in the placebo group were classified as severe. This suggests that adding vildagliptin in patients taking insulin can improve glycemia without causing excessive hypoglycemia.

A weakness of the design of this study is that it did not include patients who were receiving an insulin sensitizer, an approach that is typically taken. Given this, it is understandable that overall glycemic control was relatively poor. More effort is needed to explore the use of gliptins with insulin.

■ WHAT ROLE FOR GLIPTINS?

The evidence from the studies reviewed in this article suggests that gliptins can play an

important role in the treatment of type 2 diabetes. In certain patient groups such as the elderly, who cannot take either metformin or a thiazolidinedione and in whom concerns about hypoglycemia are greatest, thus precluding sulfonylurea therapy, gliptins may be the agents of choice. The trials reviewed here suggest that gliptins have glucose-lowering efficacy similar to that of these classes of agents. Gliptins are also effective when combined with metformin or a thiazolidinedione and, as discussed above, may prove to be useful in combination with insulin.

The eventual role of gliptins in the treatment of type 2 diabetes will depend on the answers to several questions. For example, do they preserve beta cell function and reverse the progression of diabetes? Do they affect insulin resistance? Do they have cardiovascular benefits beyond glucose-lowering? Also, since DPP-4 is widely distributed in the body, and since we do not yet know the effects of all the proteins cleaved by this enzyme, will this affect the long-term safety of these drugs?

For now, we can state with reasonable certainty that gliptins lower blood sugar levels to a degree similar to that of other oral hypoglycemic therapies, with minimal risk of hypoglycemia, with few immediate adverse effects, and without requiring dose titration. These characteristics suggest that gliptins should be considered useful agents in monotherapy and combination therapy for the treatment of type 2 diabetes.

**No increase
in gastrointes-
tinal side
effects
occurred with
vildagliptin**

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