Incretin-based therapies and their future in Type 2 diabetes mellitus

Several incretin therapies have been approved by the US FDA and/or the European Union for treatment of Type 2 diabetes mellitus (T2DM), either as monotherapy or in conjunction with diet, exercise and other T2DM therapies. Incretin-based therapies, specifically glucagon-like peptide-1 agonists, have been reported to offer a unique mechanism to lower hemoglobin A_{1c} levels by 0.4–1.1%, as demonstrated in clinical trials, and as a secondary effect reduce weight by 1–4 kg. Dipeptidyl peptidase-4 inhibitors also offer a new mechanism to reduce hemoglobin A_{1c} levels by 0.3–1.9%, as seen in clinical trials; weight loss, however, has been reported as variable. Given the projected increase in obesity and diabetes, as well as the growing evidence linking obesity and development of T2DM, incretin-based therapies may offer a future first-line agent to fight both rising sugars and rising weight.

KEYWORDS: diabetes mellitus ■ DPP-4 ■ exenatide ■ GLP-1 ■ incretin ■ liraglutide ■ saxagliptin ■ sitagliptin ■ vildagliptin

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It is estimated that 285 million people live with diabetes worldwide, a number that is projected to grow to 438 million by 2030 [101]. Type 2 diabetes mellitus (T2DM) accounts for 90% of global diabetes prevalence [102]. Although once thought to be an adult disease, T2DM has been diagnosed in morbidly obese children and adolescents in recent years [1]. The economic impact of diabetes is profound; it is estimated that the world will spend US$376 billion on diabetes care in 2010 [101]. Both prevention and the development of improved therapeutic interventions will be necessary to mitigate the effects of this quickly growing epidemic.

Obesity has been indicated as the most significant risk factor for T2DM, with up to 87% of diabetics being overweight or obese [2,3]. While T2DM reaches epidemic levels, obesity is also on the rise, with estimates indicating that 33.8% of the US population is obese (BMI ≥ 30.0 kg/m^2) [4]. The correlation between obesity and T2DM indicates the strong need for weight loss-inducing interventions in the treatment of T2DM, as even modest weight loss can lead to improved glycemic control [5,6]. While lifestyle changes, such as a healthy diet and exercise, intuitively lead to weight loss, such interventions often fail due to a lack of patient compliance [7].

Traditional antidiabetic agents do not address the role obesity plays in T2DM by inducing weight loss; in fact, sulfonylureas, thiazolidinediones (TZDs) and insulin are associated with weight gain [8]. Incretin therapies offer new hope in the treatment of T2DM. Such agents work by slowing enzymatic degradation of the gastrointestinal hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, or by mimicking endogenous GLP-1 [9]. Furthermore, incretin therapy works in a glucose-dependent manner, which significantly reduces the occurrence of hypoglycemia [10,11]. The GLP-1 agonists exenatide and liraglutide are efficacious at lowering hemoglobin A_{1c} (HbA_{1c}) and are associated with clinically significant weight loss [11,12]. The dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin, sitagliptin and vildagliptin, also efficacious at lowering A_{1c}, have not been associated with weight gain and, therefore, may serve as an alternative to oral antidiabetic agents that cause iatrogenic weight gain.

In addition to weight gain, sulfonylureas and insulin can cause hypoglycemic episodes, which not only carry significant morbidities but, if not immediately treated, can be fatal [13]. Although the risk of hypoglycemia is serious, due to the progressive nature of T2DM, sulfonylureas or insulin are often required to maintain glycemic control [14]. Incretin-based therapies have an improved safety profile when compared with these older antidiabetic agents in that they have not been associated with hypoglycemia [15].

Current treatment guidelines

Owing to apparent benefits and an increased safety profile, incretin-based therapies have been included in current treatment algorithms. The American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/

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ACE) consensus algorithm, published in October 2009, encourages early use of a GLP-1 agonist or DPP-4 inhibitor and prioritizes their use over sulfonylureas due to a reduced risk of weight gain and hypoglycemia [16,17]. The AACE/ACE consensus algorithm suggests that in combination with metformin, a GLP-1 agonist is the first-choice dual-therapy agent [16,17]. However, such guidelines encourage physicians to utilize clinical judgment and consider alternative secondary agents in appropriate cases. If a GLP-1 agonist were not desirable for a given patient, a DPP-4 inhibitor would be the next recommended option [16,17]. Despite a less favorable administration regimen, the AACE/ACE consensus algorithm gives GLP-1 agonists preference over DPP-4 inhibitors as they have a greater effect on reducing postprandial glucose excursions and carry the potential for inducing weight loss [16,17].

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus algorithm originally published in August 2006 and updated in January 2008, supports the use of GLP-1 agonists in T2DM, only as secondary therapy in clinical situations that favor its use, for example, in patients where hypoglycemia may pose an unusually increased risk or when weight loss is an important clinical consideration [18]. DPP-4 inhibitors are not included in the ADA/EASD algorithm due to the limited clinical data available at the time and relative expense [18].

Both treatment algorithms prioritize metformin as the first-choice pharmacological therapy. When metformin is contraindicated, the AACE/ACE treatment algorithm suggests that GLP-1 agonists or DPP-4 inhibitors may be used as monotherapy, while the ADA/EASD treatment algorithm encourages initiation of either a sulfonylurea or basal insulin [16,18]. According to both algorithms, GLP-1 agonists and DPP-4 inhibitors should be discontinued prior to initiating insulin therapy as concomitant use was not approved by the US FDA at the time these algorithms were published [103–106]. However, concomitant use of insulin and sitagliptin has since gained FDA approval [106]. Regardless of recommendations based on clinical guidelines, clinical trials have shown impactful data with regard to patient A_{1c} reduction and weight changes.

Clinical trials

Exenatide

Exenatide is a GLP-1 agonist incretin-mimetic therapy that was FDA approved in 2005 for the treatment of T2DM as an adjunct therapy to diet and exercise modification [19]. Exenatide has been extensively evaluated in clinical study compared with other classes of T2DM therapy, such as metformin, sulfonylurea, combination metformin–sulfonylurea therapy, TZD and insulin (TABLE 1). Exenatide has also been investigated for administration as a once-weekly formulation, although this has not yet been approved for consumer use [20].

Several clinical trials have been performed investigating the effectiveness of exenatide in comparison with the then current medication therapy [12,20–28]. A 24-week study evaluating the monotherapeutic use of exenatide twice daily at 5- and 10-µg doses exhibited a 0.7 and 0.9% reduction in A_{1c} at study conclusion and a weight loss measurement of 6.16 and 6.82 lbs, respectively [21]. Exenatide was also studied as a combination therapy, added to a pre-existing sulfonylurea regimen [22]. A 30-week trial that investigated the use of exenatide 5 and 10 µg twice daily in combination with sulfonylurea therapy observed reductions in A_{1c} of 0.46 and 0.86% and weight reductions of 1.98 and 3.52 lbs, respectively. Exenatide 5 and 10 µg twice daily in combination with metformin was also studied over a 30-week period to determine the impact on A_{1c} and weight loss [12]. When compared with placebo, the exenatide 5- and 10-µg groups were found to have a reduction in A_{1c} of 0.4 and 0.8% and a reduction in weight of 3.52 and 6.16 lbs, respectively. Exenatide has also been compared with insulin; two trials comparing the addition of exenatide 10 µg twice daily to insulin glargine found that while both maintained the same average reduction in A_{1c} (1.1–1.36%), exenatide was superior to glargine when compared for average weight change (exenatide vs glargine difference, -4.84 to -9.02 lbs) [25,26]. Exenatide is also being investigated for use as a once-weekly formulation [20]. When dosed at 2 mg once weekly compared with 10 µg twice daily over a 30-week period, exenatide has been observed to reduce A_{1c} by an additional 0.4% (both were add-on therapy to current oral T2DM therapy). While not yet available for consumer use, the formulation is expected to gain FDA approval in the year 2011.

Liraglutide

Liraglutide is a GLP-1 agonist therapy that was approved in January 2010 by the FDA for the treatment of T2DM in coordination with diet and exercise [29]. Liraglutide was extensively studied in clinical trials to determine its effectiveness when combined with other antidiabetic therapies and when compared with other

Table 1. Summary of clinical outcomes of clinical trials involving glucagon-like peptide-1 agonists.

Trial type	Length	Intervention	Baseline A_{1c} (%)	A_{1c} change (%)	Weight change (kg)	Ref.
Exenatide						
Monotherapy	24 weeks	Exenatide 5 µg twice daily	7.8	-0.7	-2.8	[21]
		Exenatide 10 µg twice daily	7.8	-0.9	-3.1	
Combination therapy	30 weeks	Exenatide 5 µg twice daily/sulfonylurea	8.5	-0.46	-0.9	[22]
		Exenatide 10 µg twice daily/sulfonylurea	8.5	-0.86	-1.6	
Combination therapy	30 weeks	Exenatide 5 µg twice daily/metformin	8.3	-0.4	-1.6	[12]
		Exenatide 10 µg twice daily/metformin	8.2	-0.8	-2.8	
Combination therapy	30 weeks	Exenatide 5 µg twice daily/metformin/ sulfonylurea	8.5	-0.55	-1.6	[23]
		Exenatide 10 µg twice daily/metformin/ sulfonylurea	8.5	-0.77	-1.6	
Combination therapy	16 weeks	Exenatide 10 µg twice daily/TZD ± metformin	7.9	-0.89	-1.6	[24]
Comparator	26 weeks	Exenatide 10 µg twice daily/metformin/ sulfonylurea	8.2	-1.1	-2.3	[25]
		Insulin glargine/metformin/sulfonylurea	8.3	-1.1	+1.8	
Comparator	32 weeks	Exenatide 10 µg twice daily/metformin or sulfonylurea	8.9	-1.36	-2.2	[26]
		Insulin glargine/metformin or sulfonylurea	8.9	-1.36	N/A	
Comparator	52 weeks	Exenatide 10 µg twice daily/metformin/ sulfonylurea	8.6	-1.0	-2.5	[27]
		Insulin aspart/metformin/sulfonylurea	8.6	-0.9	+2.8	
Comparator	20 weeks	Exenatide 10 µg twice daily/metformin	7.8	-0.9	-2.8	[28]
		Rosiglitazone 4 mg twice daily/metformin	7.8	-1.0	+3.3	
Monotherapy/ combination therapy	30 weeks	Exenatide 10 µg twice daily ± metformin ± sulfonylurea ± TZD	8.3	-1.5	-3.6	[20]
		Exenatide LAR 2.0 mg weekly ± metformin ± sulfonylurea ± TZD	8.3	-1.9	-3.7	
Liraglutide						
Monotherapy	52 weeks	Liraglutide 1.2 mg daily	8.3	-0.84	-2.05	[31]
		Liraglutide 1.8 mg daily	8.3	-1.14	-2.45	
Combination therapy	26 weeks	Liraglutide 0.6 mg daily/sulfonylurea	8.4	-0.60	+0.72	[32]
		Liraglutide 1.2 mg daily/sulfonylurea	8.5	-1.08	+0.3	
		Liraglutide 1.8 mg daily/sulfonylurea	8.5	-1.13	-0.23	
Combination therapy	26 weeks	Liraglutide 0.6 mg daily/metformin	8.4	-0.69	-1.78	[33]
		Liraglutide 1.2 mg daily/metformin	8.3	-0.97	-2.58	
		Liraglutide 1.8 mg daily/metformin	8.4	-1.00	-2.79	
Combination therapy	26 weeks	Liraglutide 1.2 mg daily/metformin/TZD	8.5	-1.48	-1.02	[34]
		Liraglutide 1.8 mg daily/metformin/TZD	8.6	-1.48	-2.02	
Comparator	26 weeks	Liraglutide 1.8 mg daily/metformin/sulfonylurea	8.3	-1.33	-1.81	[35]
		Insulin glargine/metformin/sulfonylurea	8.2	-1.09	+1.62	
Comparator	26 weeks	Liraglutide 1.8 mg daily/metformin ± sulfonylurea	8.2	-1.12	-3.24	[30]
		Exenatide 10 µg twice daily/metformin ± sulfonylurea	8.1	-0.79	-2.86	
Comparator	26 weeks	Liraglutide 1.2 mg daily/metformin ≥1500 mg daily	8.4	-1.24	-2.86	[36]
		Liraglutide 1.8 mg daily/metformin ≥1500 mg daily	8.4	-1.50	-3.38	
		Sitagliptin 100 mg daily/metformin ≥1500 mg daily	8.5	-0.90	-0.96	

TZD: Thiazolidinedione.

antidiabetic therapies, such as exenatide [30]. Liraglutide is also being investigated as a possible once-weekly therapy [107].

Liraglutide has been investigated extensively through the Liraglutide Effect and Action in Diabetes program, a series of six clinical trials investigating the use of liraglutide in combination with sulfonylureas, metformin, TZDs, exenatide or sitagliptin (TABLE 1) [30–36]. Combination therapy of liraglutide 0.6, 1.2 and 1.8 mg daily with glimepiride demonstrated an increased reduction in A_{1c} of 0.6, 1.08 and 1.13%, respectively; weight loss was only reported in the cohort receiving liraglutide 1.8 mg daily [32]. Liraglutide added to metformin therapy resulted in A_{1c} reduction of 0.69–1.00%, dependent upon dose [33]. This combination also resulted in reported weight loss of 3.92–6.14 lbs. Liraglutide in combination with metformin and/or a sulfonylurea also displayed reductions in A_{1c} and weight when compared with either insulin glargine or exenatide [30,35]. Data are not yet available for liraglutide in a once-weekly formulation, although clinical trials are still ongoing.

Sitagliptin

Sitagliptin is a DPP-4 inhibitor that is currently FDA approved for the treatment of T2DM as monotherapy in conjunction with diet and exercise or in combination with other medications for glucose management [37]. Prior to approval, sitagliptin underwent extensive clinical trials for both monotherapy and combination therapy.

When investigated as monotherapy for treatment-naive T2DM patients, sitagliptin was found in several trials to reduce A_{1c} by 0.6–0.9% (TABLE 2) [38,39]. During these trials, weight loss in the study population was found to be minimal, with a reported average loss of 0.1–0.2 lbs. Several combination therapy trials were also completed, investigating the impact of sitagliptin when added to current FDA-approved T2DM therapies (TABLE 2) [40–46]. Sitagliptin in combination with glimepiride, metformin or pioglitazone resulted in A_{1c} reduction of 0.3–1.9% after 24–30 weeks of therapy. Weight loss during these clinical trials was not always recorded, but of note was a 1.5 lb weight loss reported in one 24-week combination therapy trial of sitagliptin with metformin [44]. Sitagliptin was also investigated in combination with insulin detemir and metformin compared with sitagliptin in combination with metformin and a sulfonylurea [46]. Results from this trial reported a greater A_{1c} reduction but lesser weight reduction when sitagliptin was used in combination with insulin detemir and metformin (-1.44%, -0.8 kg, respectively) compared with sitagliptin used with metformin and a sulfonylurea (-0.89%, -1.6 kg, respectively). By contrast, a combination trial of sitagliptin with glimepiride reported an average weight gain in participants of 1.1 lbs [43].

Saxagliptin

Saxagliptin was approved for use by the FDA in 2009 for treatment of T2DM as monotherapy in conjunction with a diet and exercise regimen [47]. Prior to FDA approval, saxagliptan underwent a rigorous clinical trial program, investigating its uses as both a monotherapy and in combination therapy with metformin, sulfonylureas and TZDs.

Two large-scale clinical trials were performed to investigate the impact of saxagliptin on subject A_{1c} and weight change over a 24-week study period [48,49]. Subjects starting either trial with an A_{1c} of 7.9% or lower experienced a decrease in A_{1c} of 0.43–0.90% (TABLE 2), while subjects with an A_{1c} between 10 and 12% experienced an average decrease of 1.9%. Weight loss varied between respective dosing groups, ranging from a 1.1 lb increase to a 2.8 lb average weight loss. Combination therapy was also investigated regarding combinations of saxagliptin and metformin, glyburide and pioglitazone/rosiglitazone (TABLE 2) [50–53]. Resultant reductions in A_{1c} were greater in groups with a higher starting A_{1c} compared with other clinical trials with a lower average A_{1c}. Subjects receiving saxagliptin in combination with metformin experienced reductions in A_{1c} of 0.72–2.5%, depending on average baseline A_{1c} and saxagliptin dose [50,51]. Weight loss in the metformin trials was also reported to range from 0.5 to 1.5 lbs, dependent on treatment group. Combination therapy with either glyburide or stable pioglitazone or rosiglitazone therapy also succeeded in significantly lowering A_{1c} in their respective trials [52,53]. The average reduction in A_{1c} in these respective trials was 0.54–0.94%, while average weight gains of 1.3–1.8 lbs were also reported.

Vildagliptin

Vildagliptin is a DPP-4 inhibitor that is currently approved in the European Union for the treatment of T2DM. Approval in the USA is questionable, as a request from the FDA for additional information regarding use in patients with renal impairment was made prior to consideration for approval; since that request, it does not appear that resubmission will be made for FDA approval [108].

Table 2. Summary of clinical outcomes of clinical trials involving dipeptidyl peptidase-4 inhibitors.

Trial type	Length	Intervention	Baseline A_{1c} (%)	A_{1c} change (%)	Weight change (kg)	Ref.
Sitagliptin						
Monotherapy	24 weeks	Sitagliptin 100 mg daily	8.0	-0.6	-0.09 ± 0.2	[38]
		Sitagliptin 200 mg daily	8.1	-0.8	-0.05 ± 0.2	
	30 weeks additional	Sitagliptin 100 mg daily	7.9	-0.6	Not reported	
		Sitagliptin 200 mg daily	8.0	-0.6	Not reported	
Monotherapy	18 weeks	Sitagliptin 100 mg daily	8.0	-0.48	Not reported	[39]
		Sitagliptin 200 mg daily	8.1	-0.36	Not reported	
Monotherapy/ combination therapy	24 weeks	Sitagliptin 100 mg daily	8.9	-0.7	0.0	[40]
		Sitagliptin 50 mg twice daily/metformin 500 mg twice daily	8.8	-1.4	-0.43 ± 0.35	
		Sitagliptin 50 mg twice daily/metformin 1000 mg twice daily	8.8	-1.9	-0.43 ± 0.35	
	30 weeks additional	Sitagliptin 100 mg daily	8.7	-0.8	Not reported	
		Sitagliptin 50 mg twice daily/metformin 500 mg twice daily	8.7	-1.4	Not reported	
		Sitagliptin 50 mg twice daily/metformin 1000 mg twice daily	8.7	-1.8	Not reported	
Combination therapy	24 weeks	Sitagliptin 100 mg/pioglitazone 30–45 mg daily	8.1	-0.85	+0.82	[41]
Combination therapy	24 weeks	Sitagliptin 100 mg/metformin ≥1500 mg daily	8.0	-0.67	Not reported	[42]
	30 weeks additional	Sitagliptin 100 mg/metformin ≥1500 mg daily	7.9	-0.67	-0.41	
Combination therapy	24 weeks	Sitagliptin 100 mg/glimepiride ≥4 mg daily	8.4	-0.3	+0.5	[43]
		Sitagliptin 100 mg/glimepiride ≥4 mg/metformin ≥1500 mg daily	8.3	-0.6	+0.18	
Combination therapy	24 weeks	Sitagliptin 100 mg/metformin ≥1500 mg daily	7.5	-0.7	-0.68	[44]
Combination therapy	30 weeks	Sitagliptin 100 mg/metformin ≥1500 mg daily	9.2	-1.0	Not reported	[45]
Combination therapy	26 weeks	Sitagliptin 100 mg daily/insulin detemir/metformin	8.5	-1.44	-0.8	[46]
		Sitagliptin 100 mg daily/metformin/sulfonylurea	8.5	-0.89	-1.6	
Saxagliptin						
Monotherapy	12 weeks	Saxagliptin 2.5 mg daily	7.8	-0.72	-0.95	[48]
		Saxagliptin 5 mg daily	7.8	-0.90	-0.23	
		Saxagliptin 10 mg daily	7.8	-0.81	-1.27	
		Saxagliptin 20 mg daily	7.8	-0.74	-0.09	
		Saxagliptin 40 mg daily	7.8	-0.80	+0.5	
	6 weeks	Saxagliptin 100 mg daily	7.8	-1.09	-0.18	
Monotherapy	24 weeks	Saxagliptin 2.5 mg daily	7.9	-0.43	Not reported	[49]
		Saxagliptin 5 mg daily	7.9	-0.46	Not reported	
		Saxagliptin 10 mg daily	7.9	-0.54	Not reported	
	24 weeks	Saxagliptin 10 mg daily	10–12	-1.9	Not reported	
Combination therapy	24 weeks	Saxagliptin 2.5 mg/metformin ≥1500 mg daily	8.1	-0.73	-1.5	[50]
		Saxagliptin 5 mg/metformin ≥1500 mg daily	8.1	-0.83	-0.9	
		Saxagliptin 10 mg/metformin ≥1500 mg daily	8.1	-0.72	-0.5	
Combination therapy	24 weeks	Saxagliptin 5 mg/metformin 500 mg daily	9.4	-2.5	Not reported	[51]
		Saxagliptin 10 mg/metformin 500 mg daily	9.4	-2.5	Not reported	
Combination therapy	24 weeks	Saxagliptin 2.5 mg/glyburide 7.5 mg daily	8.4	-0.54	+0.68	[52]
		Saxagliptin 5 mg/glyburide 7.5 mg daily	8.4	-0.64	+0.81	
Combination therapy	24 weeks	Saxagliptin 2.5 mg/stable TZD therapy daily	8.3	-0.66	+0.59	[53]
		Saxagliptin 5 mg/stable TZD therapy daily	8.3	-0.94	+0.64	

TZD: Thiazolidinedione.

Table 2. Summary of clinical outcomes of clinical trials involving dipeptidyl peptidase-4 inhibitors.

Trial type	Length	Intervention	Baseline A_{1c} (%)	A_{1c} change (%)	Weight change (kg)	Ref.
Vildagliptin						
Monotherapy	52 weeks	Vildagliptin 50 mg daily	6.7	-0.2 ± 0.1	-0.23 ± 0.3	[54]
Monotherapy	52 weeks	Vildagliptin 50 mg daily	6.6	+0.1 ± 0.1	-0.5 ± 0.5	[55]
Monotherapy	24 weeks	Vildagliptin 50 mg daily	8.2	-0.8 ± 0.1	-0.82 ± 0.4	[56]
		Vildagliptin 50 mg twice daily	8.6	-0.8 ± 0.1	-0.14 ± 0.4	
		Vildagliptin 100 mg daily	8.4	-0.9 ± 0.1	-0.36 ± 0.4	
Comparator	52 weeks	Vildagliptin 50 mg twice daily	8.7	-1.1 ± 0.1	+0.14 ± 0.2	[57]
		Metformin 1000 mg twice daily	8.7	-1.4 ± 0.1	-0.86 ± 0.3	
Comparator	24 weeks	Vildagliptin 50 mg twice daily	8.7	-1.1 ± 0.1	-0.14 ± 0.2	[58]
		Rosiglitazone 8 mg daily	8.7	-1.3 ± 0.1	+0.73 ± 0.3	
Comparator	24 weeks	Pioglitazone 30 mg daily	8.7	-1.4 ± 0.1	+0.68 ± 0.3	[59]
		Vildagliptin 100 mg daily	8.6	-1.1 ± 0.1	+0.09 ± 0.3	
		Pioglitazone 15 mg/vildagliptin 50 mg daily	8.8	-1.7 ± 0.1	+0.64 ± 0.3	
		Pioglitazone 30 mg/vildagliptin 100 mg daily	8.8	-1.9 ± 0.1	+0.95 ± 0.3	
Comparator	24 weeks	Vildagliptin 50 mg twice daily	8.6	-1.4 ± 0.1	-0.18 ± 0.1	[60]
		Acarbose 100 mg three-times daily	8.6	-1.3 ± 0.1	-0.77 ± 0.2	
Combination therapy	24 weeks	Vildagliptin 50 mg/glimepiride 4 mg daily	8.5	-0.6 ± 0.1	-0.05 ± 0.3	[61]
		Vildagliptin 50 mg twice daily/glimepiride 4 mg daily	8.6	-0.6 ± 0.1	-0.59 ± 0.3	
Combination therapy	24 weeks	Vildagliptin 50 mg/metformin ≥1500 mg daily	8.4	-0.5 ± 0.1	Not reported	[62]
		Vildagliptin 50 mg twice daily/metformin ≥1500 mg daily	8.4	-0.9 ± 0.1	Not reported	
Combination therapy	24 weeks	Vildagliptin 50 mg/pioglitazone 45 mg daily	8.6	-0.3 ± 0.1	Not reported	[63]
		Vildagliptin 50 mg twice daily/pioglitazone 45 mg daily	8.7	-0.8 ± 0.1	Not reported	
Combination therapy	24 weeks	Vildagliptin 50 mg twice daily + insulin	8.4	-0.5 ± 0.1	+1.32 ± 0.7	[64]

TZD: Thiazolidinedione.

Vildagliptin monotherapy was compared in several randomized clinical trials to current FDA-approved T2DM therapies in drug-naive patients, including metformin, pioglitazone, rosiglitazone and acarbose (**Table 2**) [54–60]. Within this cohort of clinical trials, in subjects with an average baseline A_{1c} of 8.2% or higher, vildagliptin monotherapy was found to reduce A_{1c} by 0.8–1.4%. Subject bodyweight reduction was also monitored in these trials; subjects within this cohort of trials also experienced a range of weight change from +0.3 to -1.8 lbs. Clinical trials have also been performed to evaluate the use of vildagliptin as a combination therapy with pioglitazone, glimepiride, metformin and insulin (**Table 2**) [60–64]. Subjects with an average baseline A_{1c} of 8.3% or higher were found to experience a 0.5–1.0% decrease in A_{1c} when vildagliptin was added to one of the aforementioned mentioned therapies. While not monitored in all trials, weight increase was noted when vildagliptin was added to glimepiride or insulin therapies, ranging from +1.3 to -0.1 lbs.

While this discussion has included only those agents approved for use in the USA and European Union, pharmaceutical research efforts are continuing to develop several new incretin-based compounds that could impact the future of diabetes treatment. With the looming concern regarding a global increase in diabetes and obesity, continued efforts to explore multi-targeted medication therapy, such as the GLP-1 agonists, may prove to be vital in addressing the future of diabetes and obesity-based chronic disease states.

Future perspective

Excessive weight gain is a risk factor in the development of chronic diseases [109]. There is a large body of clinical evidence to suggest that being overweight or obese greatly increases the risk of developing T2DM, with a direct correlation between BMI and the incidence of T2DM diagnosis [65–70]. A patient with a BMI of 25.0–29.9 kg/m^2 is three-times more likely to be diabetic than a patient with a BMI

of less than 25.0 kg/m^2; a BMI of more than 30.0 kg/m^2 increases the likelihood of diagnosis by 20-times [67]. According to projections from the WHO, approximately 2.3 billion people will be overweight (BMI of 25.0–29.9 kg/m^2) in 2015, an increase from 1.6 billion in 2005. The global incidence of obesity (BMI ≥ 30 kg/m^2) is expected to increase from 400 million adults in 2005 to at least 700 million in 2015 [109]. This dramatic global increase in weight will most likely impact the number of people diagnosed with T2DM. The incretin-based therapies presented in this article are well positioned to expand their utility worldwide in the treatment of T2DM and obesity.

An important advantage of GLP-1 agonists in addition to A_{1c}-lowering effects is significant, sustained weight loss, while the DPP-4 inhibitors tend to be weight neutral [70–73]. Traditional treatments (i.e., sulfonylureas, TZDs and insulin) are associated with weight gain, which exacerbates insulin resistance [8]. In light of the worldwide obesity epidemic, medications to treat T2DM that result in no weight gain or weight loss may become more desirable. In addition to weight loss, GLP-1 agonists may be used as a future treatment in patients with glucocorticoid-induced diabetes. At present, data are limited so more studies are required to fully determine future use [74]. Other potential uses for GLP-1 agonists under investigation include, but are not limited to, improvement of ejection fraction in heart failure, improvement in cardiac remodeling in chronic heart failure and obesity, and weight management [75–77].

There are some practical concerns regarding the use of incretin therapy. One prominent issue is the steep prescription price of the GLP-1 agonists and DPP-4 inhibitors. At present, in the USA the average cost of liraglutide 1.2 mg and exenatide 10 µg is US$240 per month, while saxagliptin and sitagliptin are $200 per month. By comparison, metformin, glipizide, glyburide or glimepiride are all available for only $4 month. An important point to keep in mind is that while the prescription costs of sulfonureas are low, the health costs may be substantially higher considering the potential side effects and risk of hypoglycemia. When initiating therapy with GLP-1 agonists, patient compliance may be impaired or therapy may be discontinued due to gastrointestinal upset; however, this is transient and subsides after a brief period of time [19,29]. Other side effects that may occur when initiating GLP-1 agonist therapy include, but are not limited to, headache, nervousness and decreased appetite. Common side effects associated with DPP-4 inhibitor therapy may include an increased risk of upper respiratory tract infection, sore throat and diarrhea [37,47,54]. When looking to the future of this innovative class of drugs it is important to note the relatively short period of time that these medications have been on the market; exenatide was released in 2005, sitagliptin in 2006,

Executive summary

Current treatment guidelines

- The American Association of Clinical Endocrinologists recommends the use of glucagon-like peptide-1 (GLP-1) agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors early in the treatment of Type 2 diabetes mellitus (T2DM) in lieu of sulfonylureas, due to the potential for reduced weight gain and risk of hypoglycemia.
- The American Diabetes Association/European Association for the Study of Diabetes supports the use of GLP-1 agonists as secondary therapy only in situations that favor their use.

Clinical trials

- GLP-1 agonists have been observed in multiple high-powered clinical trials to effectively reduce A_{1c} as a monotherapy or in combination with other T2DM therapies and also significantly reduce weight when used in either capacity.
- DPP-4 inhibitors have been observed in multiple high-powered clinical trials to effectively reduce A_{1c} as both monotherapy and combination therapy. They have not been observed to significantly reduce weight, but are considered a weight-neutral T2DM medication at present.

Future implications

- Based on projections, worldwide obesity and development of T2DM will continue to rise over the coming century.
- Incretin-based therapies are in a prime position to help combat this epidemic as they can be used in a dual capacity if necessary to treat T2DM and help initiate weight loss.
- DPP-4 inhibitors may be more limited in their impact, but will provide a useful alternative for those patients at risk of hypoglycemia who cannot tolerate GLP-1 agonists.

Conclusion

- The possible impact that incretin-based therapies could have in the treatment of T2DM is very intriguing based on the results from clinical trials.
- Continued postmarketing evaluation must occur in order to ensure the long-term safety of these medication classes and compounds.
- While the benefits may be very lucrative in health outcomes, monetary cost may unfortunately limit the potential impact of these drugs.

saxagliptin in 2009 and liraglutide in 2010. Over the next few years, postmarketing drug safety evaluations may bring to light positive or negative impacts that incretin-based therapies may have on a larger number of patients.

Conclusion

The future utilization and market growth of the incretin-based therapies, specifically the GLP-1 agonists, looks positive. While the review of clinical data for these medications displays promise in regard to controlling A_{1c}, the weight loss specifically seen with the GLP-1 agonists make them a unique therapy for T2DM in obese individuals. Globally there are two epidemics – obesity and diabetes – that will continue to be the focus of healthcare and medication therapy. Incretin-based therapies, specifically the GLP-1 agonists, are an innovative class of medications that could potentially address both of these disease states at the same time.

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