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REVIEW

Incretin-based therapies: new treatments for type 2 diabetes in the new millennium

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Abstract: The advent of 'incretin-based therapies' – GLP-1 agonists and dipeptidyl-peptidase-4 inhibitors – which result in improvements in glycemic control comparable to those with existing oral hypoglycemic agents, and potentially improve cardiovascular and pancreatic β-cell function, represents a major therapeutic advance in the management of type 2 diabetes. Gastrointestinal adverse effects occur commonly with GLP-1 agonists, and rarely with DPP-4 inhibitors, but are dose-dependent and usually transient. The low risk of hypoglycemia, and beneficial or neutral effects on body weight, render GLP-1 agonists and DPP-4 inhibitors suitable alternatives to insulin secretagogues and insulin in overweight and elderly patients. Incretin-based therapies also improve quality of life in patients with type 2 diabetes, and may be cost-effective in the long term.

Keywords: incretin, type 2 diabetes, therapy, GLP-1, DPP-4

Introduction

Type 2 diabetes mellitus (T2DM) is well-recognized as a major problem worldwide, with substantial impacts on morbidity, mortality, quality of life, and health care costs. Because current treatment regimens for T2DM do not effectively target the fundamental defects in glucose-mediated insulin secretion and beta-cell loss, an increasing proportion of T2DM patients progress to requiring insulin. Accordingly, the recent advent of so-called 'incretin-based therapies', the incretin hormones being glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which have the potential to address these defects, represents a major paradigm shift in management.

The prevalence of T2DM has been rising dramatically, reflecting aging populations and the increasing prevalence of obesity, so that by 2025 an estimated 350 million people worldwide will be affected.[1] T2DM is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function. The last is evident initially as impaired first-phase insulin secretion in response to oral, or intravenous, glucose and progresses at a variable rate to absolute insulin deficiency, reflecting β-cell failure, which is present in a substantial number of T2DM patients at diagnosis. This defect, rather than insulin resistance, may be a primary abnormality in T2DM, particularly in Asian populations, in which postprandial hyperglycemia is often apparent before elevation of fasting plasma glucose.[1] The development, and progression, of the macrovascular (cardiovascular, cerebrovascular and peripheral vascular disease) and, particularly, microvascular

683

(nephropathy, neuropathy, retinopathy) complications of diabetes can be reduced substantially by optimizing glycemic control.[2,3] However, many patients fail to achieve the target glycated hemoglobin (HbA$_{1c}$) of ≤7% suggested by the American Diabetes Association and European Association for the Study of Diabetes, despite use of maximal doses of oral hypoglycemic agents (OHAs) in combination.[4] Moreover, concerns have recently been raised over the risk of malignancy, particularly breast cancer, with the use of sulfonylureas and insulin (especially glargine).[5]

Current therapy for type 2 diabetes

The majority of OHAs in common use are insulin sensitizers and/or insulin secretagogues. Older patients, in particular, are vulnerable to impaired awareness of hypoglycemia with consequent neuroglycopenia and adverse cardiovascular effects, dictating the need for particular caution with therapies that increase the risk of hypoglycemia. A history of severe hypoglycemia in older T2DM patients has been associated with a greater risk of dementia, which increases with the number of hypoglycemic episodes.[6] There has been considerable interest in the outcomes of the recent ADVANCE[7] and ACCORD[8] trials, which failed to show any cardiovascular benefit of lowering HbA$_{1c}$ to below 7% in patients recently diagnosed with T2DM. Significantly, in the ACCORD trial, combination therapy using high doses of thiazolidinediones (TZD), sulfonylureas (SU), metformin, and insulin, was associated with an increase in cardiovascular and all-cause mortality, possibly because of hypoglycemia. Metformin and TZDs decrease insulin resistance and hepatic glucose output, but are contraindicated in patients with significant renal and/or cardiac dysfunction, both of which occur frequently in T2DM.

There is now compelling evidence that postprandial hyperglycemia (PPG) is a dominant contributor to overall glycemia, particularly when HbA$_{1c}$ is below 8.5%,[9] and that PPG increases cardiovascular risk.[10,11] However, no current OHA specifically targets PPG, with the possible exception of α-glucosidase inhibitors such as acarbose, which decrease the rate of glucose absorption, but whose use is limited by a high prevalence of gastrointestinal adverse effects (GI AEs); and the meglitinides repaglinide and nateglinide, which are insulin secretagogues (though the risk of hypoglycemia is lower than that with sulfonylureas). Furthermore, higher doses, and combinations, of OHA are progressively required in the majority of patients.[4] The reasons for this are diverse and include difficulty in compliance with lifestyle modifications (diet, exercise) and

medications; but perhaps, most importantly, the failure of these OHAs to target several underlying pathophysiologic mechanisms of T2DM, particularly inappropriately high glucagon secretion, impaired first-phase insulin secretion, and progressive β-cell failure. Hence, the availability of drugs that stimulate insulin secretion in a physiological fashion, ie, at elevated glucose levels but not during euglycemia, are weight-neutral or promote weight loss, and have beneficial effects to preserve β-cell function, would represent a major asset in the management of T2DM. These properties are evident with recently developed medications that target the incretin system, namely the glucagon-like peptide-1 agonists and the dipeptidyl peptidase-IV inhibitors, which form the major focus of the review.

The incretin effect – implications for pathophysiology and management of T2DM

Subsequent to the discovery of insulin, La Barre reported in 1932 that a substance produced in the upper intestine had the capacity to cause hypoglycemia without stimulating exocrine pancreatic secretion, which he termed '*incrétine*' (incretin), and envisaged its use for the treatment of diabetes.[12] However, more than three decades would elapse before the 'incretin effect', ie, greater insulin release in response to an oral glucose load than an isoglycemic intravenous infusion, was demonstrated in 1964 by concurrent reports from both sides of the Atlantic.[13,14] The known incretin hormones, glucose-dependent insulinotropic polypeptide(GIP), a 42-amino acid hormone produced by K-cells in the proximal small intestine, and glucagon-like peptide-1 (GLP-1), a 30-amino acid peptide synthesized and secreted by L-cells in the ileum and colon, were not isolated until 1970[15] and 1985,[16] respectively.

In healthy people, up to 70% of post-glucose insulin secretion is mediated by incretins.[17] However, in T2DM patients, the insulin response to oral glucose is blunted in comparison to non-diabetic control subjects,[18] suggesting impairment of the incretin effect. The actions of incretins on the defects in glucose metabolism, pancreatic function and energy intake in T2DM patients are shown in Table 1. In T2DM patients during hyperglycemic clamp studies, infusion of GLP-1, but not GIP, stimulates insulin secretion,[19] establishing that the insulinotropic effect of GLP-1 is relatively well-preserved in T2DM, despite possibly lower levels, when compared to non-diabetic subjects.[20] On the other hand, GIP levels are essentially normal in T2DM but GIP-stimulated second-phase insulin secretion is

Table 1 Actions of incretins on the defects in glucose handling, β-cell function, and energy intake in type 2 diabetes patients

Defects in type 2 diabetes	Actions of incretins
Impaired glucose-stimulated insulin secretion and lack of postprandial biphasic response	Restoration of glucose-dependent insulinotropic effect and first-phase response
Hyperglucagonemia	Suppression of glucagon secretion
Defective hypoglycemia counter-regulation	Glucagon secretion, and loss of insulinotropic effect, when plasma glucose is low
Reduced β-cell mass and insulin content	Increased synthesis of proinsulin, possible increased β-cell mass or differentiation of islet precursor cells into β-cells
Accelerated β-cell apoptosis	Possible inhibition of toxin-induced β-cell apoptosis
Normal, retarded or accelerated gastric emptying	Slowing of gastric emptying
Hypercaloric energy intake, obesity	Suppression of appetite/increased satiety, weight loss

markedly diminshed[21] (although it has recently been reported that reversal of poor glycemic control in T2DM improves the insulin response to both GIP and GLP-1).[21] Hence, the development of incretin-based therapies for T2DM has hitherto focused on GLP-1, rather than GIP.

In both T2DM and healthy humans, circulating levels of intact GLP-1 decrease rapidly (half-life ~2 minutes) due to inactivation by the enzyme, dipeptidyl peptide-4 (DPP-4), such that biologically active GLP-1 represents only 10% to 20% of total plasma levels.[22] Among the truncated forms of GLP-1, GLP-1 (7–36) was found to be more potent compared to other metabolites, such as the 9–36 form.[23] The secretion of GLP-1 depends on the rate of delivery of carbohydrate to the small intestine, and is thus influenced by the rate of gastric emptying.[24] GLP-1 activates specific G-protein-coupled receptors on β-cells to stimulate insulin secretion at a threshold glucose concentration of 3.7 mmol/L, and also reduces glucose-dependent glucagon secretion, possibly in a paracrine fashion by insulin, or via GLP-1 receptors on α-cells,[25] although the precise mechanism for glucagon suppression is unknown. The role of endogenous GLP-1 in glucoregulation was established by animal and human studies – GLP-1-receptor knockout mice display impaired glucose tolerance and glucose-stimulated insulin secretion.[26] Administration of the GLP-1 receptor antagonist, exendin (9–39), inhibited postprandial insulin secretion and concomitantly increased plasma glucose in mice,[27] and accelerated gastric emptying in rats.[28] Similarly, treatment of non-diabetic human subjects with exendin 9–39 results in defective glucose-stimulated insulin secretion, reduced glucose uptake, increased glucagon levels, and, possibly, accelerated gastric emptying.[29–31] Slowing of gastric emptying may be as, if not more, important for postprandial glycemic control than stimulating insulin, given that variations in gastric emptying account for about 35% of the variance in the glycemic response to 75 g oral glucose loads in healthy subjects,[32] as well as T2DM patients.[33] The relationship of glycemia with gastric emptying is also evident for the ingestion of solid carbohydrate-containing food.[34,35]

Exogenous GLP-1 has diverse effects on pancreatic endocrine function and gut motility. Importantly, it has no significant insulinotropic effects below a glucose threshold ~4 mmol/L,[36] and the counterregulatory release of glucagon in response to hypoglycemia is preserved, even when GLP-1 is administered. Exogenous GLP-1 also stimulates insulin gene transcription and other steps in insulin biosynthesis,[37] and, in in vitro studies, has a trophic effect on β-cells by increasing proliferation and neogenesis, and inhibiting apoptosis,[38,39] which has the potential to retard or reverse β-cell failure, the fundamental defect in T2DM. In rats, GLP-1 infusion has been reported to increase insulin secretion in response to feeding, and reduce glucagon release and postprandial glycemia.[40] Exogenous GLP-1 has also been shown to inhibit energy intake and gastric emptying in rats.[41] In humans with T2DM, overnight GLP-1 infusions lowered blood glucose by restoring first-phase insulin secretion and improving β-cell function to levels that were comparable to non-diabetic subjects.[42] Preprandial boluses of GLP-1 were also effective in improving postprandial glucose levels.[43] Administration of exogenous GLP-1, resulting in supraphysiological levels in peripheral blood, stimulated glucose-mediated insulin secretion while suppressing glucagon and gastric emptying in T2DM patients with poor glycemic control.[44] In contrast, the insulin response to a carbohydrate-containing meal in healthy subjects was found to be decreased by exogenous GLP-1 in healthy subjects, because of slower gastric emptying causing lower post-load blood glucose levels.[45] In elderly T2DM patients whose OHA had been discontinued, continuous GLP-1 infusion for 12 weeks enhanced postprandial insulin secretion, and insulin-mediated glucose

disposal, while maintaining satisfactory glycemic control (HbA$_{1c}$ ~7%).[46] In another study,[47] sustained improvements of insulin secretory capacity and insulin sensitivity were accompanied by reductions in HbA$_{1c}$ (~1%) and weight (~2 kg) with supraphysiological (60 to 70 pmol/L) levels of GLP-1 maintained by 6 weeks of subcutaneous infusion. Accordingly, the mechanisms by which exogenous GLP-1 reduces postprandial glycemia in both healthy subjects and T2DM patients include delaying the entry of nutrients into the intestine, as well as increasing the insulin, and suppressing the glucagon, response to carbohydrate.

In addition to glycemic control, GLP-1 may have beneficial cardiovascular effects. Continuous GLP-1 infusion increases myocardial insulin sensitivity and glucose uptake, leading to improved left ventricular (LV) contractility, as evidenced by a significant rise in LV ejection fraction from ~30% to 40% in both non-diabetic and diabetic patients after acute myocardial infarction,[48] and in patients with chronic heart failure.[49] Perioperative (12 hours before and 48 hours after) GLP-1 infusion in T2DM patients who underwent coronary artery bypass grafting not only improved glycemic control, but also reduced hospital mortality and requirements for inotropic agents.[50] A shorter, purely postoperative (12 hours after), period of intravenous GLP-1 also improved glycemic control and reduced the need for inotropic support in a group of T2DM patients after bypass surgery.[51] Endothelial function is improved by GLP-1, which induces vasodilation in coronary artery grafts of patients with ischemic heart disease,[52] and increases flow-mediated dilatation in brachial arteries of healthy humans.[53] GLP-1 is thought to act by both GLP-1 receptor-dependent and-independent pathways, via its metabolites GLP-1 (7–36) and GLP-1 (9–36) respectively.[54]

The encouraging outcomes of studies of GLP-1 administration in T2DM have led to the development of drugs that enhance GLP-1 activity: synthetic long-acting agonists (such as exenatide and liraglutide) that are resistant to degradation by DPP-IV and could thus be administered less frequently, and inhibitors of DPP-IV (such as sitagliptin and vildagliptin) that increase endogenous GLP-1 levels. GLP-1 agonists and DPP-IV inhibitors are discussed in the following sections.

GLP-1 agonists
Exenatide (synthetic exendin-4) and exenatide LAR

Exenatide (Byetta®; Eli Lilly and Co.), an injectable GLP-1 receptor agonist, was approved by the US Food and Drug Administration (FDA) in 2005 as an adjunct therapy for T2DM patients who fail to achieve satisfactory glycemic control on metformin in combination with SU and/or TZD, and is currently available in the United States, the European Union, Australia and several Asian countries. It was developed from exendin-4, found in the saliva of the gila monster lizard,[55] has approximately 50% homology with human GLP-1, but binds more avidly to GLP-1 receptors, and is resistant to degradation by DPP-4, thus prolonging its duration of effect.[56] Exenatide is administered twice daily in a dose of 5 or 10 μg by subcutaneous injection. Reductions in fasting and postprandial glucose are mediated by the combined effects of glucose-dependent insulin secretion, suppression of glucagon release, and, in the case of postprandial glycemia, perhaps predominantly by the slowing of gastric emptying and the resulting delayed entry of nutrients into the small intestine.[57] Acutely, postprandial glucose levels are decreased by up to 75% primarily as a result of the substantial, and dose-dependent, slowing of gastric emptying,[58] associated with a reduction in plasma insulin levels in absolute terms. As a result of delayed gastric emptying (the magnitude of which differs substantially between individuals), oral medication such as contraceptive pills and antibiotics, whose efficacy depends on reaching a threshold concentration, are best taken at least an hour before exenatide.[59] As exenatide is primarily cleared by the kidneys, its use is contraindicated in patients with end-stage renal disease.[59]

Exenatide has been studied as monotherapy, as well as in combination with OHAs. In drug-naïve T2DM patients, a dose of 5 μg twice daily (bid), for 4 weeks, followed by 10 μg bid for 26 weeks, reduced mean HbA$_{1c}$ (~1%), fasting glucose (~1 mmol/L,) and weight (~3 kg), compared to non-significant reductions with placebo.[60] Three large, randomized, placebo-controlled, 30-week trials compared the efficacy and tolerability of exenatide 5 or 10 μg bid added to metformin,[61] sulfonylureas (SU),[62] or both,[63] in T2DM patients with HbA$_{1c}$ 7.5% to 11% and body mass index (BMI) 27 to 45 kg/m², who were inadequately controlled on metformin and/or SU. Exenatide 10 μg bid reduced HbA$_{1c}$ by 0.8% to 1.0%, 40% of patients achieving a HbA$_{1c}$ ≤ 7.0%. The weighted mean decrease in HbA$_{1c}$ in these studies was 1.0% (CI 0.8% to 1.2%)[64], equating to a 4.2 odds ratio for attaining HbA$_{1c}$ < 7.0%, and reductions of ~1.5 mmol/L in fasting glucose and 1.4 kg in body weight. An open-label 52-week extension of these trials in overweight patients indicated that exenatide has a sustained beneficial effect on glycemic control: ~50% of these patients achieved HbA$_{1c}$ ≤ 7% and mean weight loss was 4.4 kg

after 82 weeks.[65] Pancreatic β-cell function (assessed by the homeostasis model of assessment, HOMA) improved by 20% in T2DM patients on a TZD, with or without metformin, who were treated with exenatide, when compared to patients in whom placebo was added to their existing OHA;[66] however, this may reflect the improvement in glycemic control *per se*, rather than an absolute increase in β-cell mass or longevity. In these trials, the magnitude of the reduction in HbA_{1c} with exenatide was greater with higher pre-treatment HbA_{1c},[64] indicating greater benefits of GLP-1 agonist treatment in patients with relatively worse glycemic control. Twice-daily exenatide was also compared with insulin in an open-label trial of patients with long-standing T2DM suboptimally controlled on stable doses of OHA. Patients on exenatide and insulin glargine had comparable decreases in HbA_{1c} (~1%), with lower postprandial excursions in the exenatide group,[67] and greater reduction in fasting and 'premeal' glucose in the insulin-treated group. In addition, body weight decreased (–2.3 kg) progressively over 26 weeks in patients treated with exenatide, with significant loss (–1.9 kg) even in those who did not report nausea, and increased (1.8 kg) in patients on insulin. In a cross-over trial, HbA_{1c} fell by about 1.4% with both treatments,[68] while postprandial excursions were less and weight loss occurred with exenatide treatment. Similar trends were seen in another study comparing exenatide with premixed biphasic insulin aspart in overweight T2DM patients who were suboptimally controlled with OHA.[69] Hence, it appears that exenatide is non-inferior to insulin for glycemic control, and has the advantage of causing weight loss in obese T2DM patients.

Exenatide LAR, a long-acting release form, has been developed for once-weekly subcutaneous injection, but has not yet been marketed. In a 15-week trial of T2DM patients suboptimally controlled by metformin or diet and exercise, exenatide LAR 2 mg/week reduced mean HbA_{1c} by 1.7%, fasting glucose by ~2 mmol/L, and weight by 3.8 kg.[70] In T2DM patients with suboptimal control on diet and exercise or ≥1 OHA, this dose of exenatide LAR resulted in comparable reductions in HbA_{1c}, fasting glucose and weight after 30 weeks of treatment, with a reduced incidence and severity of nausea and other GI AEs than, exenatide 10 μg bid.[71] Exenatide LAR may produce smaller effects in postprandial glucose excursions, perhaps because inhibition of gastric emptying is less (the latter has hitherto only been assessed using the kinetics of paracetamol absorption), than twice-daily exenatide. This needs to be explored more fully, but may suggest that continuous GLP-1 receptor activation slows gastric emptying less than repeated, acute exposure to GLP-1 agonists, and may also mitigate the GI AEs. Exenatide LAR may potentially be a useful alternative for patients who are less tolerant of frequent injections, though its place in therapy remains to be determined.

Liraglutide

Liraglutide has 97% homology with GLP-1, and is longer-acting than exenatide because of an attached free fatty acid derivative that increases non-covalent binding to albumin, and renders it more resistant to DPP-4 degradation, which slows renal clearance and absorption from the subcutaneous injection site.[72] Its half-life is ~12 hours, allowing it to be administered once daily;[73] while its onset of action is slower than exenatide, it is effective and well tolerated in doses of up to 1.9 mg/day.[74,75] Liraglutide has recently been recommended for marketing authorization (under the trade name Victoza®; Novo Nordisk) as combination treatment with metformin and/or SU, or metformin ± TZD in T2DM patients with suboptimal control, by the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMEA), with final marketing authorization expected from the European Commission by June 2009.[76] Liraglutide improves glycemic control and increases insulin secretion in response to carbohydrate loads.[68–73] Effects on gastric emptying or appetite have not been observed thus far, despite its efficacy in reducing body weight. Liraglutide monotherapy for 14 weeks reduced HbA_{1c}, fasting glucose, and weight, and increased the proportion of subjects achieving $HbA_{1c} < 7\%$ compared to placebo, in a phase 2 randomized double-blind trial of patients with suboptimal control on diet or 1 OHA,[74] the greatest effects being seen with a daily dose of 1.9 mg. Phase 3 trials in the Liraglutide Effect and Action in Diabetes (LEAD) program investigated the effects of liraglutide as monotherapy, or in combination with various OHAs. A 52-week monotherapy trial (LEAD-3) demonstrated that liraglutide 1.2 mg and 1.8 mg daily led to greater reductions in HbA_{1c} and fasting glucose than glimepiride 8 mg daily.[77] In addition, body weight decreased significantly by ~2 kg in patients on liraglutide compared to a mean gain of 1 kg on glimepiride, and the incidence of minor hypoglycemia in the liraglutide group was ~10%, compared to 24% of patients on glimepiride. A 26-week comparison of the efficacy and safety of liraglutide, glimepiride, and placebo, in combination with metformin, found that liraglutide resulted in a comparative improvement in glycemic control, with weight loss and a lower incidence of hypoglycemia.[78] A 26-week, double-blind, placebo-controlled study (LEAD-4 Met + TZD)

demonstrated that liraglutide when combined with metformin and rosiglitazone was effective for glycemic control.[79] Another 26-week study found that when either liraglutide, placebo, or rosiglitazone was added to glimepiride, liraglutide produced the greatest reductions in HbA$_{1c}$ and fasting glucose[80] and adding liraglutide to glimepiride stabilized body weight. The beneficial effect of liraglutide on body weight was also seen in a trial of patients on metformin and glimepiride, which compared the addition of liraglutide (mean weight loss of 1.8 kg) with that of insulin glargine (weight gain of 1.6 kg),[81] Liraglutide-induced weight loss reflected a reduction in visceral and subcutaneous fat mass, and lean mass increased slightly.[82] Markers of β-cell function, such as the proinsulin:insulin ratio,[74] HOMA,[80] and first- and second-phase insulin responses during arginine-stimulated hyperglycemia,[83] were also improved by liraglutide. Hence, like exenatide, liraglutide is effective in improving and maintaining glycemic control as monotherapy or in combination with OHA, and in reducing body weight, with the advantage over twice-daily exenatide of requiring less frequent injections.

Safety and tolerability of GLP-1 agonists

Hypoglycemia is clearly less common with the use of GLP-1 agonists than with SU or insulin, presumably reflecting the glucose-dependent effects of the former on endogenous insulin secretion. The frequency of minor hypoglycemic episodes (about 5%) was comparable to placebo in studies of exenatide with metformin as the background therapy, though the incidence of hypoglycemia increased when exenatide improved glycemic control in conjunction with SU, and decreased in tandem with reduction in SU dose.[64] Severe hypoglycemia was rare when exenatide was combined with either metformin or TZDs.[61,63,66] The incidence of severe hypoglycemia was about 1.5% in the exenatide/glargine parallel-group comparative study,[67] but none of the episodes was severe, required medical attention or necessitated withdrawal of treatment. Minor hypoglycemia has been reported in ~10% of patients taking liraglutide as monotherapy[74] or in combination with metformin and/or TZD,[79] though the incidence is increased to ~25% when liraglutide is added to SU.[78,80]

The adverse effects of GLP-1 agonists are chiefly gastrointestinal.[58–86] Nausea is the most common with both the short-acting and LAR formulations of exenatide,[58–68] with mild to moderate self-reported nausea in ~35% of patients on exenatide 5 μg bid and up to half of the patients receiving 10 μg bid.[84] In most patients the frequency,

and severity, peaks in the first 8 weeks of treatment and decreases thereafter,[64,66] and is likely to be a central GLP-1 effect, unrelated to the slowing of gastric emptying.[84] Other GI AEs, such as diarrhea and constipation, are less common, and are also usually transient and mild. In clinical trials, treatment discontinuation because of GI AEs (nausea, vomiting, diarrhea, anorexia, abdominal pain) occurred in about 5% of patients. The risk of exenatide-induced nausea can apparently be minimized by progressive escalation in dosage.[85] The frequency of nausea may be less in patients on exenatide LAR.[70,71] Liraglutide is also associated with GI AEs, which are dose-dependent, the most common being transient mild-to-moderate nausea, which occurs in 5% to 15% of patients.[73–77] A patient-reported evaluation of GI AEs using the Gastrointestinal System Rating Scale (GSRS),[84] as part of a 14-week phase 2 trial,[74] indicated that GI symptoms are not usually severe (maximum 2 on a 7-point scale), and occur mainly in the first 2 weeks of treatment, returning to baseline thereafter. In a 26-week study of T2DM patients with suboptimal glycemic control on OHA, once-daily liraglutide was associated with less persistent nausea than twice-daily exenatide, which may be attributable to smaller fluctuations in concentration of the GLP-1 receptor agonist.[86]

Anti-exenatide antibodies are evident in about half to two-thirds of patients on exenatide,[64] or exenatide LAR,[70] but do not appear to affect either glycemic control or adverse events. A higher prevalence of injection-site discomfort and anti-exenatide antibodies were seen in patients on the LAR form. Anti-liraglutide antibodies have been detected in ~10% of patients, but, again, do not appear to have adverse effects, or influence glycemic control.[81]

GLP-1 agonists in development

New GLP-1 agonists have demonstrated improvement in fasting and postprandial glucose control in phase III trials, with apparently fewer GI AEs than currently marketed compounds. Albiglutide, a DPP-4-resistant GLP-1 analog which is administered weekly, reduced fasting and postprandial glucose levels without causing hypoglycemia in healthy subjects[87] and T2DM patients.[88] A dose of 32 mg reduced 24-hour mean weighted glucose by 35 mg/dL (~2 mmol/L) at day 2 and 56 mg/dL (~3 mmol/L) at day 9 after treatment in T2DM subjects. Of note, the frequency and severity of GI AEs of albiglutide were comparable to placebo. Taspoglutide, another once-weekly GLP-1 agonist, reduced HbA$_{1c}$ (~0.9% to 1.2%), as well as fasting and postprandial glucose levels at doses of 10 or 20 mg in T2DM, in combination with metformin for 8 weeks, with a low incidence of hypoglycemia.[89]

Weight loss was also significant, especially in the group receiving 20 mg/week (–2.8 kg).

DPP-4 inhibitors

Prevention of GLP-1 degradation by pharmacological DPP-4 inhibition in pigs,[90] and genetic inactivation in DPP-4 knock-out mice,[91] increase endogenous total GLP-1 levels, leading to increased insulin secretion and reduced fasting and post-prandial glucose concentrations. These findings have led to the development of once-daily, orally-active DPP-4 inhibitors to increase the incretin effect. DPP-4 activity is reduced by almost 100% within 15 to 30 minutes of oral administration of the DPP-4 inhibitors sitagliptin or vildagliptin, producing a 2-fold increase in mean active GLP-1 levels (to 15 to 25 pmol/L), with a duration of inhibition in excess of 16 hours because of initial rapid binding to DPP-4, followed by a slow phase of tight binding,[92] so that effects persist for 24 hours after administration of a single dose of sitagliptin[93] and vildagliptin.[94] DPP-4 inhibition increases GLP-1 and GIP levels by 2- to 3-fold, while reducing glucagon,[92] although the magnitude of the rise in GLP-1 is dependent on the type of nutrient ingested. The pharmacokinetics of sitagliptin and vildagliptin are not affected by age, gender, ethnicity or body mass index, and no significant drug interactions have hitherto been noted.[95]

Sitagliptin

Sitagliptin (Januvia®; Merck and Co, Inc.) was approved for use in a dose of 100 mg once daily, by the FDA in 2006 and subsequently in the EU, Australia and Asia, for the improvement of glycemic control in combination with metformin and/or a sulfonylurea when diet and exercise plus OHA do not result in adequate glycemic control.[96] In drug-naïve T2DM patients, sitagliptin monotherapy is more effective than placebo in reducing HbA_{1c} (by up to 1%) and fasting glucose (by up to 18 mg/dL).[97] Greater benefits in glycemic control were seen with sitagliptin 100 mg daily, compared to placebo, over a period of 24 weeks in T2DM patients already on metformin[98,99] and pioglitazone,[100] and when added to sulfonylureas (with or without metformin).[101] It was non-inferior to glipizide when added to ongoing metformin therapy.[102] Metformin stimulates GLP-1 release, increasing both active and total GLP-1 levels by 2-fold, but does not act as a DPP-4 inhibitor, and, accordingly, has a synergistic effect with sitagliptin, to increase both active GLP-1 (~4-fold).[103] A fixed-dose combination of sitagliptin and metformin (Janumet®; Merck and Co, Inc.) has recently been developed. An improvement in β-cell function has been suggested by a reduction in the proinsulin ratio and increase in insulin levels with sitagliptin, compared to placebo.[97,98,100] The effect of sitagliptin on gastric emptying has not been reported. Unlike GLP-1 agonists, sitagliptin is not associated with changes in body weight.[97–102] Sitagliptin is thus a useful add-on therapy to OHA in T2DM patients who are not overweight, especially those with suboptimal control on maximum doses of metformin. Dose adjustment of sitagliptin is recommended in patients with renal insufficiency.[104]

Vildagliptin

Vildagliptin (Galvus®; Novartis) was approved in the EU in 2008, for use in combination with metformin and/or TZD (50 mg twice daily), or with an SU (50 mg once daily), and is pending approval by the FDA.[105] Vildagliptin mono-therapy was shown to be superior to placebo in reducing HbA_{1c} (by 0.4% to 0.8%), fasting (by ~10 to 20 mg/dL) and postprandial glucose,[106] and non-inferior compared to rosiglitazone[107] in randomized, double-blinded 24-week trials. The addition of vildagliptin to metformin further improved glycemic control (HbA_{1c} reduction 0.5% to 1.2%).[108,109] The combination of vildagliptin with pioglitazone reduced fasting glucose to a greater extent than did vildagliptin or piogli-tazone alone,[110] and vildagliptin is not inferior to pioglitazone when added to metformin.[111] Vildagliptin has been shown to increase insulin and C-peptide responses to glucose by up to 100%,[108,112] suggesting improvements in β-cell function.[113] DPP-4 inhibition by vildagliptin does not apparently slow gastric emptying, possibly due to the relatively modest elevation in plasma GLP-1 levels, compared to administration of exogenous GLP-1 agonists.[114]

Safety and tolerability of DPP-4 inhibitors

Neither sitagliptin[97–102] nor vildagliptin[106–114] appear to increase the risk of hypoglycemia when used as monotherapy, or in combination with metformin or TZD, though the incidence of mild-moderate hypoglycemia was increased by approximately 2-fold to ~4% to 5% when sitagliptin was added to SU.[101,102] DPP-4 inhibitors have not been associated with significant GI AEs, and appear to be safe and well-tolerated in patients with moderate to severe renal insufficiency (including those with end-stage disease on hemodialysis) if doses are adjusted according to creatinine clearance.[115] An increased risk (odds ratio 1.34, 95% CI 1.10 to 1.64) of nasopharyngitis and all-cause infections (sinusitis, viral upper respiratory tract infections, urinary tract infections) has been observed with the use of sitagliptin,[95] and hypersensitivity reactions (anaphylaxis, angioedema and exfoliative dermatitis) have

been reported within the first 3 months of sitagliptin therapy,[96] while cases of vildagliptin-associated severe dermatological allergic reactions and elevated liver transaminases, have led to a delay in FDA approval.[105]

DPP-4 inhibitors in development

Alogliptin and saxagliptin are DPP-4 inhibitors that may be available in the near future: alogliptin is currently under FDA review, while saxagliptin is under review by the EMEA for potential marketing in late 2009. Alogliptin monotherapy is reportedly effective in reducing HbA_{1c}, as well as fasting and postprandial glucose levels in T2DM patients in doses of 25 to 400 mg daily.[116,117] In randomized, placebo-controlled, double-blinded 26-week trials, the addition of alogliptin to metformin[118] or glyburide[119] improved HbA_{1c} and fasting glucose without an increased incidence of GI AEs or hypoglycemia. Alogliptin also improved glycemic control and β-cell function in combination with pioglitazone[120] or insulin[121] in animal models. Saxagliptin reduced HbA_{1c} and both fasting and postprandial glucose levels in drug-naïve T2DM patients in a placebo-controlled, randomized, double-blind study,[122] and evidence from ongoing trials suggests that it may be effective in combination with metformin,[123] glyburide[124] or TZD.[125] Daily doses of alogliptin 12.5 to 25 mg and saxagliptin 2.5 to 10 mg lower HbA_{1c} by ~1%, which is comparable to sitagliptin and vildagliptin in doses of 50 to 100 mg daily, implying greater potency. In addition, no adverse effects attributable to disordered immune function have been reported to date for alogliptin or saxagliptin,[126] although it should be recognized that most of the clinical data available on the newer DPP-4 inhibitors have been published only in abstract form, and there is less information available about their safety profiles, in comparison with sitagliptin and vildagliptin.

Extraglycemic effects of incretin-based therapies

In addition to improving glycemic control, GLP-1 agonists may have additional beneficial effects on blood pressure (BP) and plasma lipids, in part, by effects that are apparently independent of weight loss. Exenatide 5 μg bid reduced BP by ~9 mmHg from baseline when added to existing antihypertensive therapy and OHA in obese T2DM patients during 26 weeks of treatment,[127] while mean diastolic and systolic BP (in another trial of obese T2DM patients on 5 to 10 μg bid for 82 weeks[128]) was reduced by ~4 mmHg and ~6 mmHg respectively, with the greatest reduction seen in patients who lost the most weight. Patients treated

with exenatide 5 to 10 μg bid for an average of 3.5 years demonstrated significant reductions in triglycerides (12%), total cholesterol (5%), low-density lipoprotein (LDL) cholesterol (6%), and increases in high-density lipoprotein (HDL) cholesterol (24%);[129] again, these beneficial effects were related to the magnitude of weight loss. However, a recent study using exenatide LAR[71] found that the mean reductions in systolic BP over 30 weeks (–4.7 mmHg) and diastolic BP (–1.7 mmHg) were independent of body weight. In the LEAD studies[77–80] liraglutide 1.8 mg daily for 2 weeks reduced mean systolic BP by ~2 to 4.5 mmHg, which was also apparently independent of weight loss. Liraglutide was found to lower triglyceride (TG) levels in association with reductions in weight and HbA_{1c}.[74] Other than weight reduction, the mechanisms by which GLP-1 agonists improve BP and lipids remain unclear. As discussed previously, GLP-1 analogues also have direct beneficial effects on the heart, as shown by animal studies. Both exenatide and GLP-1 (9–36) improve left ventricular performance and decreased infarct size in rat hearts during reperfusion after ischemia.[130] Liraglutide also induces significant infarct shrinkage in an ischemia-reperfusion injury murine heart preparations.[131] In T2DM patients, liraglutide reduces levels of the inflammatory markers plasminogen activator inhibitor 1, B-type natriuretic peptide and high-sensitivity C-reactive protein, which are associated with increased cardiovascular risk.[132]

There is also evidence that DPP-4 inhibitors also have beneficial effects on BP and lipids. In non-diabetic patients with moderate hypertension, sitagliptin reduced systolic and diastolic BP by ~2 mmHg, compared to placebo, within 5 days at doses of 50 to 100 mg daily.[133] Sitagliptin also reduced plasma TG by 10% to 15% and increased HDL by ~5% in doses of 25 to 100 mg daily as monotherapy over 12 weeks in T2DM patients.[134] Vildagliptin lowered total and LDL cholesterol by ~10%[135] and TG by up to 15%[122] when added to TZD in metformin-resistant patients. Possible mechanisms for the lipid-lowering effects of DPP-4 inhibitors include reduced production of intestinal TG-rich particles after fat-rich meals[136] and augmentation of lipid mobilization and oxidation,[137] although the exact mechanisms remain unclear.

Table 2 compares GLP-agonists and DPP-inhibitors.

Unresolved issues and long-term safety of incretin-based therapies

The slowing of gastric emptying induced by exogenous GLP-1 and GLP-1 agonists may cause concerns over use in T2DM patients with gastroparesis. It is now well recognized

Table 2 Comparison of GLP-1 agonists and DPP-4 inhibitors

	GLP-1 agonists	DPP-4 inhibitors
Currently marketed	Exenatide (short-acting and long-acting release), liraglutide	Sitagliptin, vildagliptin
Mode of action	GLP-1 receptor agonist, resistant to degradation by DPP-4	Inhibits degradation of GLP-1 → increases endogenous GLP-1 level
Usage	+ metformin ± SU ± TZD	+ metformin and/or TZD and/or SU
Administration	Subcutaneous injection (pen)	Oral (tablet)
Reduction in HbA$_{1c}$	~1% to 1.5%	~0.5% to 1%
B-cell function	Possibly improved	Possibly improved
Extraglycemic benefits	↓ BP ↓ Cholesterol, LDL, TG, ↑HDL ↑ Left ventricular function, arterial vasodilation (GLP-1 infusion)	↓ BP (sitagliptin) ↓ Cholesterol, LDL, TG, ↑HDL
Hypoglycemia	Very low risk	Very low risk
Weight	Reduction	Neutral
GI adverse effects	Frequent (~35% to 50%, dose-dependent and usually self-limited)	Uncommon
Gastric emptying	Slowed (greatest effect with exenatide)	No effect
Other adverse effects	Pancreatitis	Nasopharyngitis, upper respiratory tract infection, headache; elevated liver enzymes (vildagliptin)

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SU, sulfonylureas; TG, triglycerides; TZD, thiazolidinediones.

that gastric emptying (GE) is delayed in perhaps 30% of patients with long-standing T2DM,[32] and correlates poorly with the presence and severity of upper GI symptoms.[138] In healthy subjects the magnitude of the slowing of GE by exogenous GLP-1 is sufficient to cause 'gastroparesis' in ~50%,[45] and in T2DM patients the slowing of GE by exenatide is greater when GE is relatively faster.[58] It is also known that in diabetics with vagal neuropathy, unlike healthy subjects, exogenous GLP-1 fails to relax the proximal stomach.[139] The implications are that the magnitude of the reduction in postprandial glycemia induced by GLP-1 is likely to depend on GE, and that in patients with autonomic neuropathy-associated gastroparesis (whether symptomatic or not), any further slowing of gastric emptying is likely to be minimal. Both of these hypotheses warrant formal evaluation. Patients with symptomatic gastroparesis have been excluded from the majority of trials of GLP-1 agonists – hence, the issue of whether these drugs exacerbate, or have no effect on symptoms, also remains unresolved.

Post-marketing cases of acute pancreatitis have rarely been reported with exenatide;[140] however, T2DM patients have a ~3-fold increased risk of pancreatitis,[141] as well as other risk factors for pancreatitis including gallstones, obesity, ethanol abuse and severe hypertriglyceridemia. Eight out of the nine reported cases of pancreatitis in the LEAD program occurred in patients on liraglutide.[142] Studies in animals to evaluate this issue have hitherto failed to clarify whether there is a causal

association between pancreatitis and the use of incretin-based therapies. Administration of metformin, sitagliptin, or liraglutide did not increase transcription of genes associated with pancreatitis in mice, and GLP-1 receptor knockout mice did not differ from normal mice in the severity of experimentally induced pancreatitis when treated with exenatide.[143] However, treatment with sitagliptin and metformin was associated with increased pancreatic ductal turnover, ductal metaplasia, and one case of pancreatitis in rats.[144]

The non-GI AEs associated with sitagliptin and vildagliptin may be related to the immunological properties of DPP-4, which is expressed in many tissues, and has numerous substrates, including GI hormones, neuropeptides, and cytokines.[145] As DPP-4 is known to be involved in immunoregulation as a T-cell costimulator, and in breakdown of cytokines such as bradykinin and interleukin-2 and -1β,[146] inhibition of DPP-4 may have adverse effects on immune function. Indeed, the severity of rheumatoid arthritis has been reported to be inversely related to DPP-4 activity,[147] and DPP-4 levels are reduced in nasal tissue of patients with chronic rhinosinusitis.[146] Although DPP-4 inhibition is known to reduce the levels of the cardioprotective GLP-1 metabolite GLP-1 (9–36) which is cleaved from native intact GLP-1, there is hitherto no evidence of adverse cardiovascular effects.[101–118] As clinical trials involving sitagliptin and vildagliptin evaluated use for a maximum of only 52 weeks, more long-term safety data are required, particularly in view

of the need for chronic treatment in T2DM, and the presence of DPP-4 in multiple organ systems.

Cost-effectiveness and patient-centered outcomes of incretin-based therapies

The cost-effectiveness of exenatide, compared to OHA or insulin, has been evaluated in several studies. As add-on therapy to metformin, it is cost-effective compared to pioglitazone and glibenclamide,[59] and also as monotherapy in drug-naïve patients compared to metformin alone. An analysis, based on data from 314 overweight T2DM patients who completed an 82-week trial of exenatide,[65] projected that 30 years of treatment with exenatide added to OHA would be cost-effective in comparison to a hypothetical placebo arm,[148] in terms of improvements in clinical outcomes (glycemic control, weight, BP, and lipids) with concomitant reductions in the risk of micro- and macrovascular complications, increased life expectancy, and improved quality of life. These were associated with incremental cost-effectiveness ratios (ICER) of US$35,571/life-years gained, and US$36,133/quality-adjusted life-year, below the threshold ICER of US$50,000. Using data from the same cohort, a study projected models of long-term complications, life expectancy, quality-adjusted life expectancy, and direct medical costs of patients on exenatide versus those on insulin glargine in the United Kingdom (UK),[149] and concluded that exenatide was associated with a lower cumulative incidence of most cardiovascular (CVD) complications, including CVD-related death, and was more cost-effective than glargine. However, this study based its analyses on estimated costs of exenatide which ranged from 20% to 100% of the US price (US$161/28 days). Another UK study, which used the actual UK National Health System price of exenatide (~£68/28 days), rather than an estimated cost, found that exenatide was less cost-effective than glargine in a 40-year projection.[150] It is evident that the cost-effectiveness of exenatide in relation to insulin glargine is highly dependent on the relative prices of these medications, which vary substantially between countries.

Patient-reported measures, such as quality of life and treatment satisfaction, have also been analyzed, using data from a 26-week randomized, open-label study comparing exenatide to insulin glargine in T2DM patients with suboptimal glycemic control on metformin and sulfonylurea.[67] This analysis included 228 patients on exenatide and 227 on insulin, with outcomes measured by 5 scales: 1) Diabetes Symptom

Checklist (frequency and perceived discomfort of physical and psychological symptoms associated with diabetes); 2) Diabetes Treatment Flexibility Scale (focusing on patient choices in meals and daily activities); 3) Diabetes Treatment Satisfaction Questionnaire (satisfaction with current treatment regimen); 4) EuroQol-EQ5D (overall health status); and 5) vitality scale of the SF-36 (energy level and fatigue). Both exenatide and insulin groups showed significant improvement from baseline in symptoms, satisfaction with treatment, overall health status, and energy levels.[151] The authors noted that although exenatide was associated with GI AEs and increased frequency of injections, these did not result in less patient satisfaction, which they attributed to the benefits of weight loss in this treatment group. Hence, the benefits of exenatide therefore appear to outweigh adverse effects, weight loss in particular conferring an advantage over insulin. At present, there are no cost-benefit analyses available for liraglutide.

In relation to the DPP-4 inhibitors, a cost-effectiveness analysis compared the addition of sitagliptin, rosiglitazone or SU to metformin in patients with $HbA_{1c} > 6.5\%$.[152] Local health surveys in Austria, Finland, Portugal, Scotland, Spain, and Sweden were used to generate average patient profiles for the analysis, using data on clinical and adverse effects from two recent trials of sitagliptin.[102,153] Adding sitagliptin was found to be a more cost-effective alternative to the addition of rosiglitazone or an SU, incremental cost-effectiveness ratio values ranging from €5949/QALY to €20 350/QALY, depending on the individual country. However, these studies may not be generalizable to countries outside the EU, because of differences in health care costs and prices of medication. Analysis of the cost-effectiveness of vildagliptin is not currently available.

Given the comparable outcomes of the use of GLP-1 agonists and DPP-4 inhibitors in T2DM for many parameters, their cost-effectiveness is an important issue. An analysis compared estimated six-month total, and diabetes-related, medical costs among 2482 patients on sitagliptin, with 1885 patients on exenatide, in the US.[154] Exenatide was associated with lower total 6-month direct medical costs (US$9340 vs US$9995), despite some component costs being higher with exenatide, ie, those associated with diabetes-related drugs, and diabetes-related medical care including emergency room attendance. Sitagliptin was associated with higher outpatient costs. This study concluded that use of the GLP-1 agonist was associated with higher diabetes-related costs, but lower total medical costs than the DPP-4 inhibitor; however, as with comparisons of incretin therapies with conventional injectable

and oral medications, the results of this cost-benefit analysis cannot be extrapolated to outside the US.

The place of incretin-based therapies in the treatment of T2DM and impaired glucose tolerance

The American Association of Clinical Endocrinologists (AACE) currently advocates DPP-4 inhibitor monotherapy for T2DM patients with HbA_{1c} 6% to 7%, or in combination with metformin or TZD if target HbA_{1c} ($\leq$6.5%) is not achieved, and adding a GLP-1 agonist to SU, metformin, and/or TZD in patients who do not achieve target HbA_{1c}.[155] In contrast, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) did not recommend, in their combined consensus statements on standards of medical care in diabetes[156] and initiation and adjustment of treatment in T2DM,[4] either GLP-1 agonists or DPP-4 inhibitors as first- or second-tier treatments, despite acknowledging the weight-lowering effect of exenatide, and the utility of exenatide and sitagliptin for improved postprandial glycemic control with an associated low risk of hypoglycemia. It should be recognized that selected groups of patients may benefit from early, or even first-line, use of incretin-based therapies. The weight-lowering effect of GLP-1 agonists is beneficial in the overweight and obese, especially since many add-on therapies (sulfonylurea, TZD and insulin) promote weight gain. As discussed, trials using exenatide reported a dose-dependent reduction in body weight by up to 4.5 kg in at least 30 weeks.[55–65]

GLP-1 agonists may also have a role in the management of critically ill patients with T2DM, in whom both hyperglycemia and hypoglycemia are risk factors for a poor outcome. GLP-1 infusion appears to reduce plasma glucose significantly in association with increased insulin and suppressed glucagon concentrations, without the risk of hypoglycemia in severely ill patients who were hyperglycemic while receiving total parenteral nutrition,[157] as well as in fasted diabetic patients who had undergone major surgery.[158] More recently, GLP-1 infusion has been shown to markedly attenuate the glycemic response to enteral nutrition (arguably the preferred route of nutritional support) in non-diabetic critically ill patients, reflecting its insulinotropic and glucagonostatic properties.[159] These observations suggest that GLP-1 and/or its agonists have a potential role in the management of hyperglycemia in the critically ill, without the attendant risks of insulin-induced hypoglycemia. The latter were emphasized by the results of the NICE-SUGAR study, in which the use of insulin infusions to achieve target blood glucose 4.5 to 6.0 mmol/L was shown to increase both hypoglycemia and mortality in critically ill patients.[160]

Although DPP-4 inhibitors are weight-neutral and do not significantly reduce appetite, their lack of GI side effects compared to GLP-1 agonists and metformin, and low risk of hypoglycemia, render them especially suitable for the management of T2DM in older patients, in whom the polypharmacy often required for glycemic control is accompanied by increased risks of hypoglycemia and other adverse effects due to age-related changes in drug metabolism, reduced energy intake, and comorbidities such as cardiovascular and renal impairment. In particular, sulfonylureas are associated with a high risk of hypoglycemia accounting for substantial morbidity and health-care costs in this group.[161] Studies of sitagliptin[97,98,162] and vildagliptin[106,107,111,163] including subjects $\geq$65 years of age, and patients with moderately severe hepatic[164] and renal[165] impairment, suggest that the DPP-4 inhibitors are as effective (HbA_{1c} reduction ~1%) and well-tolerated as in younger patients. The DPP-4 inhibitors were also associated with a low incidence (~1%) of severe hypoglycemia, and GI and other adverse events such as peripheral edema (2% to 10%).

Conclusions

Despite the relatively recent advent of GLP-1 agonists and DPP-4 inhibitors, evidence has rapidly accumulated to support their efficacy and safety in the management of T2DM, as well as their potential for improving cardiovascular and β-cell function. The low risk of inducing hypoglycemia, and beneficial or neutral effects on body weight, render them attractive alternatives to insulin secretagogues and insulin as add-on therapy to metformin, or even as first-line therapy in selected groups of patients, especially in the overweight and the elderly. Incretin-based medications are likely to be increasingly at the forefront of therapy of T2DM in the new millennium.

Disclosures

The authors declare no conflicts of interest.

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