Linagliptin: new DPP-4 inhibitor for type 2 diabetes mellitus

Zin Htike *MRCP and* ***Ian Lawrence*** *FRCP*

KEY POINTS

- **linagliptin (Trajenta) is indicated for treating type 2 diabetes mellitus to improve glycaemic control in adults:**

  as monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment

  as combination therapy combined with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control, or combined with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control
- **formulated as a 5mg film-coated tablet taken once daily; 28=£33.26**
- **no dosage adjustment required in renal or hepatic impairment or in the elderly**
- **in clinical trials treatment with linagliptin 5mg as monotherapy resulted in a placebo-corrected mean change in HbA_{1c} of -0.69 per cent**
- **trials of linagliptin 5mg as an add-on therapy also showed a modest and sustained improvement in glycaemic control**
- **linagliptin was well tolerated in all the clinical studies; hypoglycaemic events were rare and mild**
- **linagliptin provides a modest improvement in glycaemic control without an increased risk of hypoglycaemia or weight gain and is a useful option in patients with declining renal function**

Linagliptin is a new DPP-4 inhibitor licensed for use as monotherapy or in combination in type 2 diabetes. Our New products review presents the clinical data relating to its efficacy and adverse events and considers its place in treatment, particularly in patients with renal impairment

Type 2 diabetes mellitus (T2DM) is a chronic disorder characterised by progressive decline in beta cell function and insulin resistance leading to deterioration of glycaemic control. When glycaemic goals are not achieved with lifestyle modification, the current consensus in managing T2DM is to adopt a stepwise approach in adding oral glucose-lowering agents followed by insulin therapy.[1,2]

However, treatment with oral antidiabetic agents (OADs) is associated with undesirable side-effects such as GI intolerance, weight gain, peripheral oedema, osteoporotic fracture or hypoglycaemia.[3,4] Moreover, the use of OADs either alone or in combination is limited by their inability to sustain glycaemic control over time.[5]

When the combination of OADs fails to achieve glycaemic targets, the conventional approach is to add insulin.[1,2] Intensification of insulin therapy invariably results in weight gain.[1,6]

Thus new glucose-lowering agents that can achieve or maintain glycaemic control without weight gain are a welcome addition to existing agents in the treatment of T2DM.

Role of incretin-based therapies

In healthy individuals, oral glucose ingestion stimulates the production of gut hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), collectively known as incretins. Of these two hormones, GLP-1 potentiates glucose-dependent insulin

	DPP-4 inhibitors	GLP-1 analogues
Also known as	incretin enhancers	incretin mimetics
Approved drugs to date	sitagliptin, saxagliptin, vildagliptin, linagliptin	exenatide, liraglutide, Bydureon (exenatide once weekly)
Mechanism of action	inhibit DPP-4 enzyme and prolong the action of GLP-1	structurally similar to human GLP-1 and increase availability of GLP-1
Relation to endogenous GLP-1 level	depends on availability of endogenous GLP-1	independent of endogenous GLP-1
Increase in level of GLP-1	physiological range	supraphysiological range
Route of administration	oral	subcutaneous injection
Reduction of HbA_{1C}	0.6–0.8%	0.8–1.5%
Effect on body weight	neutral effect or minimal weight loss	weight reduction approximately 1.5–3kg
GI side-effects	less common	more common

Table 1. Comparison of DPP-4 inhibitors and GLP-1 analogues

secretion, restores first-phase insulin response, suppresses inappropriately high glucagon secretion, delays gastric emptying and promotes satiety leading to weight loss.[7,8]

Physiologically, insulin response is greater with oral than parenteral glucose administration, a phenomenon known as the incretin effect.[9] In patients with T2DM, this effect is impaired with the reduction of GLP-1 concentration, although biological potency is maintained.[8,10] Moreover, GLP-1 is rapidly inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme, which is found abundantly in the vascular endothelium of intestinal lining. Hence GLP-1 action is short lived with a half-life of one to three minutes.

Thus, agents that could either mimic or prolong GLP-1 action become an attractive therapeutic option in the management of T2DM.

Recently, two novel classes of incretin-based therapies have emerged, incretin mimetics and incretin enhancers (see Table 1). Incretin mimetics are GLP-1 analogues that act on GLP-1 receptors, and incretin enhancers inhibit the DPP-4 enzyme and prevent GLP-1 degradation, thereby increasing its availability.

The National Institute for Health and Clinical Excellence (NICE) has recommended the use of DPP-4 inhibitors as a second-line therapeutic option in addition to either metformin or a sulfonylurea (dual therapy) or as a third-line option in combination with metformin and a sulfonylurea (triple therapy).[2]

The purpose of this article is to review the safety and efficacy of using a novel class of DPP-4 inhibitor, linagliptin (Trajenta), in the management of T2DM.

Pharmacokinetics and pharmacodynamics of linagliptin

Linagliptin was approved in 2011 for use in the management of T2DM. It is structurally distinct from other currently available DPP-4 inhibitors – saxagliptin (Onglyza), sitagliptin (Januvia) and vildagliptin (Galvus) – in that it is derived from a xanthine-based compound and functionally by reversibly and competitively binding to DPP-4 enzymes with high selectivity and high affinity.[11,12]

Bioavailability of linagliptin is approximately 30 per cent lower than that of sitagliptin (87 per cent) or vildagliptin (85 per cent).[13] Once absorbed, it binds extensively to plasma protein in a concentration-dependent manner, which contributes to its long half-life (113–131 hours) and hence sustained inhibition of DPP-4 activity.

When co-administered, linagliptin has shown no significant interaction with metformin.[14] Similarly, there is no significant interaction with other OADs (pioglitazone or glibenclamide) or drugs commonly used in cardiac disorder (warfarin or digoxin).[15,16]

Moreover, linagliptin does not interfere with CYP enzymes and is unlikely to affect the agents metabolised by this system.[11] Thus, it is safe to use concomitantly with drugs such as rifampicin, ketoconazole or diltiazem without the need to adjust the dose.[17]

Efficacy of linagliptin

The safety and efficacy of linagliptin was assessed in both

phase 2 and phase 3 clinical trials. In a phase 2 clinical study, treatment with linagliptin 5mg once daily provided the greatest reduction in HbA_{1c} of -0.37 per cent compared to that of 2.5mg (-0.31 per cent) or 10mg (-0.28 per cent) over a 28-day period.[12]

The efficacy of linagliptin as a mono or combination therapy in phase 3 clinical trials is discussed below and summarised in Table 2.

As monotherapy

In a multicentre, randomised, parallel-group, double-blinded trial involving 503 T2DM patients with a baseline HbA_{1c} of ≥8 per cent, the efficacy of linagliptin 5mg was compared with placebo.[18] Patients who were pretreated with an OAD underwent a wash-out period of six weeks including a placebo run-in period in the last two weeks before randomisation. Those who were not taking any treatment also underwent the placebo run-in.

Treatment with linagliptin 5mg resulted in a placebo-corrected mean change in HbA_{1c} of -0.69 per cent ($p<0.001$) at 24 weeks. A greater proportion of patients in the linagliptin treatment arm achieved a reduction in HbA_{1c} of ≥0.5 per cent (47 *vs* 19 per cent, odds ratio – OR=4.2, $p<0.001$). At the end of the study period, both fasting plasma glucose (FPG) and two-hour postprandial glucose (PPG) improved by -1.3 and -3.2mmol per litre respectively ($p<0.0001$).

As add-on therapy

Linagliptin 5mg as an add-on therapy in T2DM patients whose control was inadequate on either metformin alone[14] or a sulfonylurea[19] demonstrated a modest but significant and sustained improvement in glycaemic control over 24 and 18 weeks respectively (see Table 2). In the former study, there was a statistically significant improvement in

Study	Duration of study (weeks)	Number of subjects	Treatment and comparators	Baseline mean HbA_{1c} (%)	Change in HbA_{1c} (%) from baseline	Placebo-subtracted change in HbA_{1c} (%)	*p*-value
Del Prato *et al*[18]	24	503	linagliptin (5mg) placebo	8.0	-0.44 +0.25	-0.69	<0.0001
Taskinen *et al*[14]	24	700	linagliptin (5mg) + metformin (1500mg) placebo+ metformin (1500mg)	8.1	-0.49 +0.15	-0.64	<0.0001
Lewin *et al*[19]	18	245	linagliptin (5mg) + SU placebo + SU	8.6	-0.54 -0.07	-0.47	<0.0001
Owen *et al*[20]	24	1058	linagliptin (5mg) + metformin + SU placebo + metformin + SU	8.1	NS	-0.62	<0.0001
Gomis *et al*[21]	24	389	linagliptin (5mg) + pioglitazone (30mg) placebo + pioglitazone (30mg)	8.6	-1.06 -0.56	-0.51	<0.0001
Gallwitz *et al*[22]	104	1519	linagliptin (5mg) + metformin (1500mg) glimepiride (1-4mg) + metformin	7.7	-0.16 -0.36		

NS = not stated in the abstract

Table 2. Summary of randomised controlled trials with linagliptin

Study	Duration of study (weeks)	Number of subjects	Treatment and comparators	Baseline mean HbA_{1c} (%)	Change in HbA_{1c} (%) from baseline	Placebo-subtracted change in HbA_{1c} (%)	*p*-value
Cooper *et al*[26] (pooled analysis of 3 RCTs)*	24	2141	linagliptin (5mg) *vs* placebo	8.0–8.3	-0.63 (GFR ≥80ml/l)	NR	<0.0001
			linagliptin (5mg) + metformin (1500mg) *vs* placebo + metformin (1500mg)		-0.69 (GFR 50–<80ml/l)		<0.0001
			linagliptin (5mg) + metformin + SU *vs* placebo + metformin + SU		-0.69 (GFR 30–<50ml/l)		=0.0174

NR = not relevant
*normal to moderate renal impairment, no significant intergroup difference, p=0.865

Table 3. Summary of pooled analysis of trials in patients with normal to moderate renal impairment in T2DM patients

both FPG with a treatment difference of -1.2mmol per litre and two-hour PPG of -3.7mmol per litre when compared to placebo. In both studies, more patients in the linagliptin arm achieved target HbA_{1c} <7 per cent.

When linagliptin was added as a triple therapy to a combination of metformin and a sulfonylurea in T2DM patients with insufficient glycaemic control over a 24-week duration, the placebo-adjusted mean reductions in HbA_{1c} (-0.62 per cent) and FPG (-0.70mmol per litre) were found to be significantly greater than addition of placebo.[20] Patients with baseline HbA_{1c} of ≥7 per cent were 3.6 times more likely to achieve a target HbA_{1c} <7 per cent. There was no significant difference in body weight in all the above studies.[14,19,20]

Combination therapy of linagliptin (5mg) with pioglitazone (30mg) in a 24-week study also revealed a significant and clinically meaningful improvement in glycaemic control from baseline compared to pioglitazone monotherapy.[21] There was a significant difference in placebo-subtracted mean change in FPG of -0.8mmol per litre (p<0.0001) between the two groups.

In general, DPP-4 inhibitors have a neutral effect on weight. However, when used in combination, weight gain was found to be greater in the linagliptin and pioglitazone combination than pioglitazone treatment alone, 2.3 *vs* 1.2kg (p=0.014). However, the combination offered an additional -0.5 per cent reduction in HbA_{1c}.

A head-to-head trial comparing the efficacy of linagliptin (5mg) with that of glimepiride (1–4mg) as an add-on therapy to metformin over two years demonstrated non-inferiority of linagliptin to glimepiride, with reductions in HbA_{1c} of -0.16 and -0.36 per cent respectively. Mean body weight decreased with linagliptin but increased with glimepiride, with a difference in adjusted mean body weight of -2.9kg (p<0.001) favouring treatment with linagliptin.[22]

In a meta-analysis of cardiovascular (CV) events from eight phase 3 studies (n=5239), primary CV events (defined as a composite of CV death, stroke, MI and hospitalisation for unstable angina) occurred in 11 (0.3 per cent) patients receiving linagliptin and 23 (1.2 per cent) receiving comparators (placebo, glimepiride, voglibose). The hazard ratio (HR) was significantly lower in patients receiving linagliptin (HR 0.34, 95% CI 0.16–0.70), supporting the hypothesis that linagliptin may have CV benefits in patients with T2DM.[23]

Safety and tolerability

The most commonly reported adverse events in the above studies were nasopharyngitis, hypertension, back pain and headache. GI side-effects are rare.[14,18] In all the studies linagliptin was found to be well tolerated either alone or in combination.[14,18,19–21] In a dose-ranging study, the frequency of adverse events and tolerability profile were similar and comparable to that of placebo across all active dosing groups.[12,24]

Since the action of linagliptin is driven by oral glucose ingestion,

it has low propensity to induce hypoglycaemia, which is reflected in the clinical trials. It was uniformly reported in all the studies that hypoglycaemic events were mild and rare with linagliptin treatment.

Cardiovascular safety

In the UKPDS study, improvement in glycaemic control was shown to reduce the onset and progression of microvascular complications.[6] However, the effect on macrovascular complications remains debatable. Reassuringly, a recently presented safety analysis of a two-year comparison of linagliptin and glimepiride in metformin-treated patients has demonstrated a 50 per cent relative risk reduction of composite cardiovascular events.[22]

Renal acceptability

One of the microvascular complications of T2DM is the development of diabetic nephropathy, with progressive decline in renal function. Management of T2DM in renal impairment is challenging as treatment options are limited, and the majority of the therapeutic agents are either contraindicated or not recommended in moderate to severe renal impairment.

Linagliptin is the only DPP-4 inhibitor that has a primarily nonrenal route of excretion,[25] while 90 per cent of sitagliptin and 22 per cent of vildagliptin is excreted unchanged via the kidney. Thus, it offers a potential therapeutic option in the management of T2DM patients with renal impairment.

The effect of renal function on efficacy and safety of linagliptin was evaluated in a large pooled analysis of three randomised placebo-controlled phase 3 trials involving 2141 T2DM patients with normal to moderate renal impairment (see Table 3).[26] The study concluded that linagliptin provided a reliable HbA_{1c} reduction (-0.63 to -0.69 per cent) and a safety profile irrespective of renal function at 24 weeks.

Place in therapy

In the UK, DPP-4 inhibitors are recommended by NICE as either a second- or third-line option in the management of T2DM. Linagliptin has consistently been shown to provide a modest and sustained improvement in glycaemic control without an increased risk of hypoglycaemia or weight gain in all the studies mentioned above. It is generally well tolerated with minimal GI side-effects.

Moreover, it is found to be safe to use in patients with renal impairment. Treatment with linagliptin 5mg once daily may provide a safe and efficacious therapeutic option in patients with declining renal function with the convenience of not requiring dose adjustments or periodic drug-related kidney function monitoring.[26] Thus linagliptin is likely to be a valuable treatment option for T2DM patients with insufficiently controlled hyperglycaemia in whom renal function is impaired.

The distinctive mechanism of action, predominantly nonrenal elimination pathway and favourable safety profile of linagliptin may offer advantages over existing therapies in the treatment of T2DM. However, the findings from long-term studies are awaited to safeguard its safety and efficacy.

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Declaration of interests

Dr Htike and Dr Lawrence have received honoraria and/or support to attend academic meetings from several pharmaceutical companies, including Boehringer Ingelheim.

Dr Htike is specialty registrar and Dr Lawrence is consultant physician in the Department of Diabetes & Endocrinology, The Leicester Royal Infirmary