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Combination of Linagliptin and Metformin for the Treatment of Patients with Type 2 Diabetes

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ABSTRACT: Type 2 diabetes mellitus (T2DM) is a progressive condition requiring long-term treatment. Most patients with T2DM are unable to maintain normoglycemia using metformin alone; thus, combination therapy is a pivotal part of disease management. Addition of the dipeptidyl peptidase-4 inhibitor linagliptin, with its proven efficacy, low propensity for hypoglycemia, and weight neutrality, has been shown to improve glycemic control for patients who are not well controlled with metformin. As patients often have other comorbidities requiring pharmacotherapy, an increase in pill number, different prescribing frequencies, and timing of medications may adversely impact patients' adherence. Studies have shown that treatment nonadherence contributes to increased morbidity, mortality, and healthcare cost. In the United States, the single-pill combination (SPC) of linagliptin/metformin is available in three strengths approved for twice-daily administration: 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg. The SPC has the potential to reduce pill burden and simplify patients' treatment regimens, thereby promoting improved adherence and efficacy.

KEYWORDS: dipeptidyl peptidase-4 inhibitor, combination therapy, metformin, single-pill combination

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Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disease that includes decreased pancreatic insulin secretion, increased peripheral insulin resistance, increased hepatic glucose production, impaired lipolysis, gastrointestinal incretin deficiency/resistance, α-cell hyperglucagonemia, increased renal glucose reabsorption, and neurotransmitter dysfunction.[1] It follows that a therapeutic approach targeting a single defect is unlikely to achieve normoglycemia or slow progression of the disease. In conjunction with lifestyle modifications, metformin is the recommended first-line pharmacotherapy for most patients.[2,3] Continuous loss of β-cell function prevents a large proportion of individuals from achieving or maintaining normoglycemia with metformin alone, necessitating the addition of another antihyperglycemic agent with a complementary mechanism of action.

Dipeptidyl peptidase (DPP)-4 inhibitors are good candidates for combination therapy with metformin because of their different glucose-lowering mechanism, proven efficacy, low propensity for hypoglycemia, and weight neutrality. Among the available DPP-4 inhibitors, linagliptin stands out as the only agent predominantly excreted through biliary pathways, making it suitable for patients with any degree of renal or liver impairment without dose adjustment. The addition of linagliptin to metformin in a loose-pill combination (LPC) has provided better glycemic control than monotherapy with either

metformin or linagliptin alone.[4–9] Linagliptin, like other DPP-4 inhibitors, is available as a single-pill combination (SPC) with metformin. In the United States, linagliptin/metformin SPC is available in three different dosages approved for twice-daily use: 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg.[10] In the European Union, two approved strengths are available for twice-daily use: 2.5/850 mg and 2.5/1000 mg.[11] This review discusses the clinical evidence for linagliptin and metformin combination and the place of the SPC in T2DM therapy.

Place of DPP-4/Metformin Combination Therapy in T2DM Guidelines

Currently available treatment guidelines from the American Diabetes Association (ADA)/European Association for the Study of Diabetes,[2] the American Association of Clinical Endocrinologists (AACE),[3] the International Diabetes Federation (IDF),[12] and the United Kingdom's National Institute for Clinical Excellence (NICE),[13] recognize metformin as a first-line therapy because of its efficacy, low risk of hypoglycemia, and weight loss. Recommendations regarding the agents to be added when treatment needs to be intensified are less specific. The IDF and NICE guidelines mention sulfonylureas (SU) ahead of DPP-4 inhibitors. The ADA does not prioritize second-line agents, but stresses individualization of therapy.[2] The AACE algorithm lists glucagon-like peptide (GLP)-1 agonists and DPP-4 ahead of thiazolidinediones (TZD) and SUs.[3] Moreover, some guidelines call for initial combination therapy for patients with levels of glycated hemoglobin (HbA_{1c}) ≥7.5%[3] or ≥9.0%.[2,3] SPCs are not specifically recommended because guidelines do not highlight formulations.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile of Linagliptin and Metformin

Linagliptin and metformin exert their glucose-lowering effects through complementary mechanisms. Linagliptin inhibits the DPP-4 enzyme, thus prolonging the half-life of the intestinal incretins, GLP-1 and gastric inhibitory polypeptide. This results in enhanced glucose-dependent insulin secretion and decreased glucagon production, leading to an overall improvement in glucose homeostasis both in the fasting and post-prandial state.[14] In addition, preclinical data have shown that linagliptin, via its incretin-enhancing effects, can slow disease progression by preserving pancreatic β-cell mass and function.[15,16] The mechanism of action of metformin is independent of insulin secretion and occurs mainly through inhibition of hepatic gluconeogenesis[17,18] and improved peripheral insulin sensitivity.[19] Its glucose-lowering effects can be observed in the fasting state after overnight inhibition of gluconeogenesis.[12,13] Moreover, metformin increases GLP-1 production in obese patients with and without T2DM, and a recent study confirmed that metformin monotherapy increases GLP-1 levels postprandially independent of DPP-4 activity.[20] Thus, the use of the linagliptin/metformin SPC may lead to a further increase in GLP-1 levels, potentially resulting in additive or synergistic glucose-lowering effects.

Pharmacokinetic/Pharmacodynamic Studies on Linagliptin and Metformin Alone and in Combination

Several studies have assessed the pharmacokinetic and pharmacodynamic properties of linagliptin and metformin alone and in combination.[21] In a randomized crossover study of 16 male subjects, linagliptin 10 mg once daily (QD) and metformin 850 mg three times daily were each given alone and in combination. Coadministration of both agents had no clinically relevant effects on the pharmacokinetics and pharmacodynamics of either agent.[22] Because linagliptin monotherapy is administered once daily, whereas metformin is administered twice daily, assessment of the pharmacodynamics and pharmacokinetics of linagliptin administered twice daily was required to facilitate development of the SPC. A 7-day crossover study in 16 healthy subjects showed bioequivalent exposure and similar DPP-4 inhibition with linagliptin 2.5 mg twice daily (BID) when compared with linagliptin 5 mg QD.[23] Furthermore, the bioequivalence of three linagliptin/metformin SPC strengths and the corresponding combination of loose pills (linagliptin 2.5 mg plus metformin 500 mg, 850 mg, or 1000 mg) was evaluated in three separate prospective, randomized, open-label, single-dose, two-way crossover studies in healthy volunteers (n = 287).[24] The 90% confidence intervals (CI) of the adjusted geometric mean ratios of the maximum plasma concentration and the area under the plasma concentration–time curve were within bioequivalence acceptance limits of 80% to 125%. The authors concluded that SPCs of linagliptin plus metformin are bioequivalent to the individual tablets.[24] Another study showed that food does not have a clinically relevant effect on the administration of linagliptin/metformin SPCs.[25]

Clinical Evaluation of Linagliptin/Metformin LPC

Findings from clinical trials of linagliptin and metformin administered as LPCs show significant improvements in HbA_{1c} and fasting plasma glucose (FPG) compared with metformin alone. The safety profile of the LPC was similar to that of placebo and metformin, with a low risk of hypoglycemia and weight neutrality. These trials include patients across a wide spectrum of hyperglycemia, with baseline HbA_{1c} levels ranging from >7.0% to ≤12.0%.

Linagliptin as add-on to metformin compared with placebo. The addition of linagliptin to metformin in patients with T2DM whose glycemia is not well controlled on monotherapy has been assessed in several clinical studies.[4,6,7] In a dose-ranging study, 333 patients were randomized in a double-blinded fashion to linagliptin (1, 5, or 10 mg QD), placebo, or open-label glimepiride (1–3 mg QD) for 12 weeks. Placebo-corrected HbA_{1c} levels were −0.73% and −0.67% for 5 and 10 mg of linagliptin, respectively, compared with −0.9%

for glimepiride. The only hypoglycemic events reported occurred in glimepiride patients (n = 3).[4] In a 24-week, randomized, placebo-controlled study of patients inadequately controlled on metformin (≥1500 mg/day), addition of linagliptin 5 mg resulted in clinically and statistically significant placebo-corrected reductions in HbA_{1c} (–0.64%), FPG (–1.2 mmol), and 2-hour postprandial glucose (–3.7 mmol/L). Hypoglycemia was rare, occurring in three patients receiving linagliptin and five patients receiving placebo; the authors attribute this difference to the glucose-dependent actions of linagliptin. Body weight of these patients did not change significantly from baseline.[7]

In addition to the studies of once-daily add-on linagliptin, Ross et al[6] evaluated if linagliptin 2.5 mg BID provided comparable efficacy and safety to linagliptin 5 mg QD when added to metformin BID (maximum dose 1500 mg/day) in 491 patients with T2DM and inadequate glycemic control. After 12 weeks, mean placebo-adjusted reductions in HbA_{1c} were –0.74% for linagliptin 2.5 mg BID and –0.80% for linagliptin 5 mg QD, with a treatment difference of 0.06. Thus, linagliptin 2.5 mg BID had non-inferior HbA_{1c}-lowering effects when compared with linagliptin 5 mg QD, with comparable safety and tolerability. The incidence of hypoglycemia was low.

Linagliptin as add-on to metformin compared with SU. In a 2-year, parallel-group, non-inferiority study, patients with T2DM receiving metformin background therapy were randomized to either linagliptin 5 mg (n = 777) or glimepiride (1–4 mg; n = 775) QD.[5] Reductions in adjusted HbA_{1c} levels were similar in both groups (linagliptin, –0.16%; glimepiride, –0.36%) and met the non-inferiority criterion. The incidences of hypoglycemia (58 of 776 [7%] vs 280 of 775 [36%] patients, $P < 0.0001$) and cardiovascular (CV) events (12 vs 26 patients; relative risk 0.46, 95% CI 0.23–0.91) were significantly lower in the linagliptin group than those in the glimepiride group. The currently ongoing Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA®) trial is the largest head-to-head CV outcome trial, to date, that directly compares an SU (glimepiride) with a DPP-4 inhibitor (linagliptin). This study will provide a unique perspective with respect to CV outcomes with these two commonly used agents.[26]

Initial combination of linagliptin and metformin. Initial combination therapy may be advantageous in treating T2DM, as it targets the numerous pathophysiologic defects early.[11] In a 24-week study, 791 patients were randomized to one of the six treatment regimens: (1) linagliptin 2.5 mg plus metformin 500 mg BID, (2) linagliptin 2.5 mg BID plus metformin 1000 mg BID, (3) metformin 1000 mg BID, (4) metformin 500 mg BID, (5) linagliptin 5 mg QD, or (6) placebo.[8] Mean placebo-corrected reductions in HbA_{1c} were –1.7% (linagliptin + high-dose metformin), –1.3% (linagliptin + low-dose metformin), –1.2% (high-dose metformin), –0.8% (low-dose metformin), and –0.6% (linagliptin). Thus, initial combination therapy with linagliptin plus metformin was superior to metformin or linagliptin monotherapy with respect to efficacy and had a comparable safety profile. Subgroup analyses of placebo-corrected HbA_{1c} change by baseline HbA_{1c} (Table 1) indicated that the efficacy response to initial combination therapy was greater in randomized patients with higher baseline HbA_{1c} levels (8.5% ≤ HbA_{1c} <11.0%) than with moderate HbA_{1c} levels (HbA1c <8.5%). These findings were strongly corroborated by the large HbA_{1c} reduction of –3.7% in the open-label cohort (baseline HbA_{1c} ≥11.0%).[8] In a 1-year extension of this study, patients previously in treatment groups 1 to 3 continued their regimen (non-switched, n = 333), whereas patients in treatment groups 4 to 6 were re-randomized to one of the three continuing regimens (switched, n = 233). Patients in the non-switched group maintained HbA_{1c} reductions over the 1.5-year period (–1.63%, –1.32%, and –1.25%, respectively) for treatment groups 1, 2, and 3. Patients in the switched groups showed additional HbA_{1c} reductions.[9] Subgroup analyses of unadjusted HbA_{1c} change by baseline for the non-switched group indicated that the efficacy response was greatest in patients with higher baseline HbA_{1c} levels (≥9%) compared with those with moderate levels (HbA_{1c} 8.0% to <9.0%). Notably, only 14 of 31 patients with baseline HbA_{1c} levels ≥9% remained in the metformin monotherapy group at the end of the extension trial (Table 2).[9]

A recent 24-week study was conducted in adults newly diagnosed with T2DM who were randomized to linagliptin 5 mg QD (n = 157) or linagliptin 5 mg QD plus metformin BID (uptitrated to a maximum of 2000 mg/day; n = 159).

Table 1. Adjusted placebo-corrected mean change in HbA_{1c} at week 24 by HbA_{1c} category at baseline in randomized patients and open-label arm patients.[8]

HbA_{1c}	MEAN CHANGE IN HbA_{1c}, % (n)					
	LINA 5 mg QD	MET 500 mg BID	MET 1000 mg BID	LINA 2.5 mg + MET 500 mg BID	LINA 2.5 mg + MET 1000 mg BID	OPEN-LABEL ARM*
<8.5%	–0.37 (66)	–0.75 (68)	–1.01 (74)	–1.18 (63)	–1.47 (66)	–
8.5% to <11%	–0.77 (69)	–0.78 (73)	–1.37 (64)	–1.49 (74)	–1.93 (74)	–
≥11%	–	–	–	–	–	–3.7 (66)

Notes: *Patients in the open-label arm were treated with linagliptin 2.5 mg + metformin 1000 mg BID: observed cases (n = 48).
Abbreviations: BID, twice daily; HbA_{1c}, glycated hemoglobin; LINA, linagliptin; MET, metformin; QD, once daily.

Table 2. Mean change in HbA_{1c} at week 54 by baseline HbA_{1c} in the non-switched set.[9]

MEAN CHANGE IN HbA_{1c}, % (n)			
HbA_{1c}	MET 1000 mg BID	LINA 2.5 mg + MET 500 mg BID	LINA 2.5 mg + MET 1000 mg BID
>8.0% to <9.0%	–1.15 (28)	–1.20 (21)	–1.50 (35)
>9.0%	–2.26 (14)	–2.15 (21)	–2.74 (20)

Note: Treated set, observed cases, n, at week 54.
Abbreviations: BID, twice daily; HbA_{1c}, glycated hemoglobin; LINA, linagliptin; MET, metformin.

HbA_{1c} reductions with linagliptin monotherapy and initial combination with metformin were –2.02% and –2.81%, respectively; the difference was statistically significant. An HbA_{1c} reduction of ≥0.5% after 24 weeks was achieved by 81.4% and 93.9% of patients receiving linagliptin monotherapy versus the combination, respectively. Hypoglycemia occurred in 3.2% and 1.9% of patients, respectively.[27]

Triple combinations with linagliptin and metformin. Metformin in combination with linagliptin has been studied in triple therapy regimens with SUs and TZDs. In a 24-week study of patients with T2DM inadequately controlled with metformin and SU, the addition of linagliptin significantly improved glycemic control (placebo-corrected change: HbA_{1c}, –0.62%; FPG, –0.7 mmol/L). Symptomatic hypoglycemia occurred in 16.7% and 10.3% of linagliptin and placebo groups, respectively; severe hypoglycemia was reported in 2.7% and 4.8% of those with hypoglycemia, respectively.[28] In another phase 3, randomized, placebo-controlled study, linagliptin was administered to patients with T2DM inadequately controlled with metformin and pioglitazone.[29] After 24 weeks, linagliptin produced significant and clinically meaningful improvements in glycemic control (placebo-corrected change: HbA_{1c}, –0.57%), largely attributed to the results in the Asian population (HbA_{1c}, –0.90%). Investigator-reported hypoglycemia occurred in 5.5% and 5.6% of linagliptin- and placebo-treated patients, respectively. It should be noted that certain countries, including Germany, do not reimburse for the use of pioglitazone because of its potential adverse effects. Metformin plus a DPP-4 inhibitor may be preferred over metformin plus SU or TZD. This is because SUs carry a risk of weight gain and hypoglycemia, and their CV safety has been questioned; and TZDs are associated with bone fractures, weight gain, fluid retention in predisposed patients, and bladder cancer.[3] The combination of a DPP-4 inhibitor with an SU carries a risk of hypoglycemia and thus may require a lower dose of SU.[30] Nonetheless, triple therapy using SUs and TZDs may be necessary for select patients. Studies assessing efficacy and safety of triple combinations with new agents, such as sodium-glucose co-transporter-2 inhibitors, are needed. Although it is attractive to have three different modes of action in a single pill, many questions remain open.

Place of SPCs in Therapy

Although combination therapy is aimed at targeting multiple, complementary pathways for normalizing glucose levels, it can add to a regimen's complexity. An SPC provides a reduced pill burden and simplified dosage regimen, which is an advantage over separately administered medications that may facilitate improved adherence. Non-adherence to long-term treatment is one of the leading causes of increased morbidity, mortality, and healthcare cost.[31] Improved adherence with SPC use has been demonstrated in a number of clinical studies.[32–34] For example, in a retrospective cohort analysis of prescription claims in Italy, adherence was better in patients prescribed an SPC compared with those prescribed monotherapy or LPCs.[34] A systematic review of data from seven studies that compared SPCs with LPCs of the same agents found 13% improved adherence with the SPC regimen.[32] Additionally, patients inadequately controlled on monotherapy converting from mono- or LPC therapy to an SPC regimen have demonstrated improved adherence rates of 23% and 16%, respectively.[33]

Better adherence often results in better efficacy, as demonstrated in a retrospective study using data from nearly 6000 European patients with T2DM, where the use of SPCs resulted in 0.25% of lower HbA_{1c} levels.[35] Similarly, a greater reduction in HbA_{1c} was seen in patients receiving either glyburide plus metformin as an SPC (–2.02%) versus an LPC (1.49%).[36] Several other retrospective cohort studies have demonstrated improved glycemic efficacy of SPC over loose-pill regimens. In one such study of medication usage from an administrative pharmacy claims database, patients receiving metformin/glyburide SPC experienced greater reductions in HbA_{1c} than those receiving the LPC, especially when baseline HbA_{1c} was ≥8%, despite lower medication doses in the SPC regimen.[36,37] A retrospective analysis of 11,000 diabetic patients in a managed-care organization demonstrated that each 25% increase in adherence to antidiabetic agents was associated with a 0.05% decrease in HbA_{1c}.[38] Moreover, a number of studies have demonstrated that the tolerability profile of SPCs is comparable to that of an LPC regimen.[39] Two meta-analyses[32,40] that compared medication adherence, treatment adherence, patient satisfaction, and cost of SPCs versus LPCs showed that SPC use was associated with significantly greater HbA_{1c} reduction[40] and improved adherence versus LPCs (+10% to 13%) and for those switching to an SPC (+3.5% to 12.4%).[32]

Patient preference is another important factor in the successful treatment of chronic diseases and is affected by daily pill burden, increased complexity of a treatment regimen, and

potential side effects. A cross-sectional survey of patients with T2DM showed that next to hypoglycemia, medication-related weight gain and CV risks were significant concerns for many patients, and thus, these were the predictors of likely medication non-adherence.[41] The SPC of linagliptin/metformin is associated with a low risk of hypoglycemia and no clinically relevant weight gain, which should translate into good patient acceptability and adherence. Additionally, patients preferred SPCs and used fewer healthcare resources, resulting in lower direct monthly costs, compared with patients on LPCs.[32]

Cost effectiveness is an important issue with both individual agents and combination therapy. SPCs have the potential to lower costs indirectly and directly. Indirect savings are created by improved adherence and reduced long-term risk of complications and hospitalizations. In an analysis of seven studies, an inverse relationship between hospitalization costs and adherence was shown.[42] Additionally, a retrospective study of >100,000 patients with T2DM showed that annual healthcare costs were increased by $336 and $1509 for non-adherent metformin and SU users, respectively, compared with adherent patients.[43] With respect to the cost of medication, an analysis of data of Texas Medicaid recipients revealed that branded SPCs were less expensive than branded individual agents.[44] However, branded SPCs are likely to cost more than generic individual agents; for combinations involving three oral agents, the costs may be higher than the cost of insulin therapy and would have to be individually evaluated.

In summary, the advantages of the linagliptin/metformin SPC include greater HbA1c reduction versus individual components alone, a similar tolerability profile, the availability of different dosage strengths for maximal dosing flexibility, and greater convenience for the patient. These characteristics may translate into improved adherence, better glycemic control, and greater cost-effectiveness. On the other hand, the combination of linagliptin with metformin in an SPC also offsets some of the advantages of linagliptin monotherapy, such as once-daily dosing and no dosing adjustment in patients with renal impairment. Because metformin needs to be administered twice daily, so does the linagliptin/metformin SPC, with the linagliptin dose of 5 mg split between the two doses. Moreover, while linagliptin can be used without dosage adjustment in patients with chronic kidney disease (CKD), a characteristic that sets it apart from all other DPP-4 inhibitors, renal excretion of metformin is prolonged in these patients, and thus, contraindicated in those with serum creatinine levels above the upper limit of normal for their age. This limits the use of the linagliptin/metformin SPC in a large proportion of patients with renal impairment. There is debate surrounding the question of whether the definition of CKD provided in the metformin United States label (creatinine ≥1.5 and ≥1.4 mg/dL for men and women, respectively) and European Union label (creatinine clearance, <60 mL/min) is too restrictive and whether patients with mild-moderate renal impairment could benefit from using metformin in future.[45]

In conclusion, the linagliptin/metformin SPC addresses different aspects of T2DM pathophysiology through complementary mechanisms, as recommended in the current diabetes guidelines. Randomized clinical trials of linagliptin used in conjunction with metformin demonstrate significant improvements in HbA_{1c} measures and FPG compared with administration of monotherapy, with a low risk of hypoglycemia and weight neutrality. The approval of the linagliptin/metformin SPC, like other SPCs, was based on these combination trials as well as bioequivalence studies. Real-world evidence from healthcare databases supports the efficacy of SPC over loose pills in improving adherence and decreasing HbA_{1c}. Future iterations of T2DM guidelines would benefit from practical pointers on the place of SPC in therapy.

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Conceived and designed the experiments: TH. Analyzed the data: TH. Wrote the first draft of the manuscript: TH. Contributed to the writing of the manuscript: TH. Agree with manuscript results and conclusions: TH. Jointly developed the structure and arguments for the paper: TH. Made critical revisions and approved final version: TH. The author reviewed and approved of the final manuscript.

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