Linagliptin is associated to increased treatment adherence and satisfaction in elderly outpatients with diabetes and advanced chronic kidney disease

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Abstract

The treatment of diabetes in frail elderly patients with decreased renal function is challenging and insufficiently supported by evidence. Due to their good tolerability and low hypoglycemic risk, oral dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a reasonable option for glycemic control in the elderly. The aim was to evaluate the efficacy and safety of linagliptin, a long acting, oral DPP-4 inhibitor with a predominantly non-renal elimination route, in elderly patients with severe chronic kidney disease (CKD). This was a retrospective, observational study in outpatients with type 2 diabetes and advanced-stage CKD (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) referring to a diabetes clinic in Italy. Patients were switched from basal insulin to oral linagliptin 5 mg once daily and observed for 14 months. Assessed variables included glycemic control (HbA1c target, 7.5%-8.0%), adherence to treatment (Morisky questionnaire) and patient satisfaction (*diabetes treatment satisfaction questionnaire*). Adverse events, including hypoglycemic episodes, were also recorded. Thirty patients [mean (±standard deviation) age 70.2 (±8.2) years, HbA1c 7.6% (±0.3), fasting blood glucose 173.9 (±23.5) mg/dL] with type-2 diabetes and advanced CKD were included. The switch to linagliptin did not affect significantly glycemic control, was well tolerated and associated with a reduction in hypoglycemic episodes. Adherence to treatment was better with linagliptin than basal insulin and patient satisfaction significantly improved after switching. Linagliptin appears as a valid option for glycemic control in elderly diabetes patients with severe CKD in treatment with low-dose insulin. However adequately designed long-term studies are needed to confirm these findings.

Introduction

Diabetes largely affects the elderly population, with a prevalence of approximately 25%.[1-3] According to an analysis performed by the Italian Association of Clinical Diabetologists (AMD), 60% of the 414,814 patients with type 2 diabetes who referred to national diabetes centers in 2009 were older than 65 years.[4] Treatment of elderly patients with diabetes is challenging because of the high prevalence of comorbidities, diabetes complications, polypharmacy and frailty.[2] In addition geriatric syndromes including cognitive dysfunction, functional impairment, depression, falls with fractures and persistent pain may negatively affect health outcomes and self-care abilities.[5,6] The substantial under-representation of patients older than 65 years in randomized clinical trials regarding glucose-lowering treatments and thus the lack of evidence guiding therapeutic decisions is an additional issue in the management of diabetes in this age group.

Diabetes is one of the main causes of chronic kidney disease (CKD), a common diabetes-related complication in elderly patients.[7] Besides being associated with higher mortality and impaired quality of life, CKD increases the risk of hypoglycemia by contributing risk factors such as altered drug metabolism, drug-drug interactions, albuminuria, autonomic neuropathy, anorexia, malnutrition, infections, associated cardiac and hepatic disease and impaired renal glucose release.[8] Hypoglycemia, in turn, has detrimental effects also on cardiovascular disease and cognitive functions.[5,9] CKD further complicates diabetes treatment.[7,10] Effective glycemic control delays the deterioration in kidney function,[11] however many glucose-lowering medications are contraindicated or require dose adjustments in elderly diabetes patients with renal impairment.[12] In the elderly, glucose lowering therapies, even when aimed at a carefully tailored glycemic target, may result in adverse events, including hypoglycemia and hypotension. The attitude of older patients towards treatment and their preferences should be also taken into account when selecting a treatment.[5] Indeed a priority for many elderly patients is the maintenance of their independence, self-care ability and quality of life.[13] As a consequence, especially in older patients, diabetes treatment should be tailored to individual needs and expectations.[5] This is partly reflected in current national and international guidelines for the management of diabetes, which recommend the use of individualized glycemic targets in the elderly to optimally balance potential benefits and risks of treatment.[2,14-16] While the general target of glycated hemoglobin (HbA1c) levels <7% might be still reasonable for certain elderly patients, less stringent targets (*e.g.*, HbA1c <7.5%-8.0%) might be more appropriate for frail, older patients, including those with severe CKD.[2,14,15,17]

Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged in recent years as a class of oral glucose-lowering agents suitable for elderly patients, since they are generally well tolerated, have a low risk for hypoglycemia and lack significant drug interactions.[2,14,18,19] DPP-4 inhibitors stimulate the release of insulin in a glucose-dependent manner by counteracting the inactivation of incretins.[18,20] Linagliptin is a potent, long-acting DPP-4 inhibitor approved for the treatment of type 2 diabetes mellitus as monotherapy or as combination therapy with other oral antidiabetic agents or insulin.[21] Unlike the other DPP-4 inhibitors, linagliptin is eliminated mainly by routes other than the renal pathway: it can thus be administered even to patients with renal impairment with no dose adjustments.[22,23]

In phase 3 studies in patients with type 2 diabetes aged up to 80 years, linagliptin showed clinically relevant glucose-lowering effects, with a low frequency of hypoglycemia.[24-28] In a recent 24-week, randomized,

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placebo-controlled trial in patients aged ≥70 years, linagliptin (5 mg once daily) in addition to the existing glucose-lowering treatment was associated with a clinically meaningful improvement in glycemic control;[3] notably, the efficacy of linagliptin was not influenced by age, renal impairment, or diabetes duration.

The main goal of this retrospective observational study was to evaluate the efficacy and tolerability of linagliptin in low-dose insulin-treated type-2 elderly diabetes patients with advanced CKD after switching from basal insulin. Adherence to treatment and treatment satisfaction were also investigated.

Materials and Methods

Study design and patients

This was a retrospective observational study, which involved elderly outpatients with type 2 diabetes and advanced CKD [estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2, according to the modification of diet in renal disease equation] referring to an antidiabetic unit in Italy [*SSD di Malattie Metaboliche e Diabetologia, Ospedale 'E. Profili', Fabriano (AN), Italy*]. All patients were previously treated with low-dose basal insulin (<20 U/day). When linagliptin became available in Italy, patients were switched to oral linagliptin, 5 mg once daily, as monotherapy and then observed for 14 months. Linagliptin treatment was initiated according to the licensed indication and to the Italian guidelines for the management of patients with diabetes.[14,21] The primary objective of the study was to evaluate the efficacy of linagliptin in lowering plasma glucose and HbA1c levels. The secondary objective was to determine safety of linagliptin and patient adherence and satisfaction with the new treatment.

Treatment

Before switching to linagliptin, patients had been in treatment with low-dose basal insulin (<20 U/day). Patients were switched to oral linagliptin (Trajenta®, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) 5 mg/day, because other oral hypoglycemic drugs are contraindicated or not recommended in elderly diabetes patients with severe CKD.[14] According to current guidelines for the treatment of frail elderly patients, including those with advanced-stage CKD, a less aggressive glycemic target was used, namely HbA1c between 7.5 and 8%.[14,17] If glycemic control with linagliptin monotherapy was insufficient, patients were allowed to add basal insulin.

Assessments

Patients were visited at baseline (study entry and beginning of the treatment with linagliptin), and after 2, 8, and 14 months from the beginning of the treatment with linagliptin. The efficacy of linagliptin in ensuring glycemic control was evaluated based on the changes in plasma glucose levels from baseline to 2, 8, and 14 months. At each time point, three measurements of plasma glucose were made: before taking any food (fasting plasma glucose), then 2 h after breakfast and 2 h after lunch (postprandial plasma glucose). HbA1c levels were also measured at each study visit.

Adherence to treatment was assessed during a face-to-face interview of each patient with a psychologist at baseline and after 14 months, using a modified version of the four-item, self-reported Morisky medication adherence scale.[29] A total score of 0 indicates high adherence, 1-2 medium adherence, and 3-4 low adherence.

Patient satisfaction with linagliptin was assessed at baseline and after 14 months by using the validated Italian version of the *diabetes treatment satisfaction questionnaire* (DTSQ).[30,31] The DTSQ questionnaire includes 8 items, 6 of which (items 1, 4, 5, 6, 7 and 8) are summed up in a single score ranging from 0 (very dissatisfied) to 36 (very satisfied). The remaining 2 items are treated individually and assess the perceived frequency of hypoglycemic and hyperglycemic episodes.

For the evaluation of safety and tolerability, patient reported adverse events were recorded. The frequency of hypoglycemic episodes was also recorded.

Statistical analysis

Categorical variables are presented as percentage and continuous variables as mean values ± standard deviation (SD). Continuous variables were compared by Student's *t*-test or by Wilcoxon's test for non-parametric paired data. For all analyses statistical significance level was set at P values <0.05. Statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Thirty patients [53.0% female, mean (±SD) age 70.2 (±8.2) years] with type 2 diabetes and severe CKD were included in this study. Their baseline characteristics are shown in Table 1. The mean HbA1c level was 7.6% (±0.3) and mean fasting blood glucose level was 173.9 (±23.5) mg/dL. Four patients (13.3%) were on hemodialysis, 3 (10.0%) on peritoneal dialysis and 2 (6.7%) were transplant recipients. Three patients were lost to follow-up.

Over the 14 months of observation, mean blood glucose and HbA1c levels did not change significantly from baseline (Figure 1). Mean (±SD) HbA1c levels were 7.6% (±0.2), 7.7% (±0.3), and 7.7% (±0.3) at 2, 8 and 14 months, respectively. At the end of the study, the majority of patients (24/27, 88.9%) were able to maintain stable blood glucose levels and HbA1c values with linagliptin monotherapy, while 3 patients (11.1%) required the addition of basal insulin (glargine) to achieve and maintain glycemic values within the target.

Assessment of adherence to treatment based on the Morisky questionnaire showed that at baseline 67% of patients could be classified as highly adherent with insulin (score of 0), 30% as moderately adherent (score of 1-2) and 3% as poorly adherent (score of 3-4). After the switch to oral linagliptin, 85% of patients were found to be highly adherent, 15% were moderately adherent, while no patient wad classified as non-adherent (Figure 2A).

The switch to linagliptin was associated with a statistically significant increase from baseline in patient satisfaction with their treatment. At baseline, the mean (±SD) DTSQ score was 17.19 (±3.44). After 14 months of treatment with linagliptin, the mean DTSQ score was 31.48 (±2.71) (P<0.001) (Figure 2B).

Patient perception of high blood sugar levels (item 2 of DTSQ questionnaire) was lower (even if not significant) with linagliptin in comparison to baseline (1.96±0.81 *vs* 2.33±0.83). After the switch to oral linagliptin, patients also reported significantly less perception of low blood sugar levels (item 3 of DTSQ questionnaire) compared with baseline (1.48±0.58 *vs* 2.15±1.13, P<0.05). The treatment with linagliptin was well tolerated by our vulnerable patients. Nobody reported adverse events during the 14 months of observation, or interrupted treatment due to adverse events. In particular, there was no report of hypoglycemic events over the 14 months of treatment with linagliptin, while in the three months preceding the switch to linagliptin 5 patients (16.7%) experienced a hypoglycemic event during the treatment with insulin.

Discussion

This observational study in elderly diabetes patients with advanced CKD shows that the switch from basal insulin to oral linagliptin (5 mg once daily) was well tolerated and allowed patients to maintain, for more than 1 year, fairly stable plasma glucose levels and to keep HbA1c levels within the target values of 7.5%-8.0% recommended for frail, older subjects. The majority of patients (88.9%) achieved this degree of glycemic control with linagliptin alone. The addition of basal insulin to linagliptin was needed only in a minority of patients. Notably, the switch to linagliptin was associated to a decrease of frequency of hypoglycemia, as well as better compliance with

Table 1. Demographic and baseline characteristics (n=30).

Age, years	**70.2±8.2 (51-83)**
Sex, n (%)	
Female	16 (53.0%)
Male	14 (47.0%)
BMI, kg/m²	**24.1±2.6 (19.4-28.8)**
Plasma glucose level, mg/dL	
Before taking any food (FBG)	173.9±23.5
2 h after breakfast (PPG)	197.4±25.7
2 h after lunch (PPG)	206.8±28.8
HbA1c %	**7.6±0.3**
Patients with severe CKD, n (%)	
On hemodialysis	4 (13.3)
On peritoneal dialysis	3 (10.0)
Transplant recipients	2 (6.7)

Unless otherwise indicated, data are presented as mean values ± standard deviation (range). BMI, body mass index; FBG, fasting blood glucose; PPG, postprandial blood glucose; CKD, chronic kidney disease; HbA1c, glycated hemoglobin.

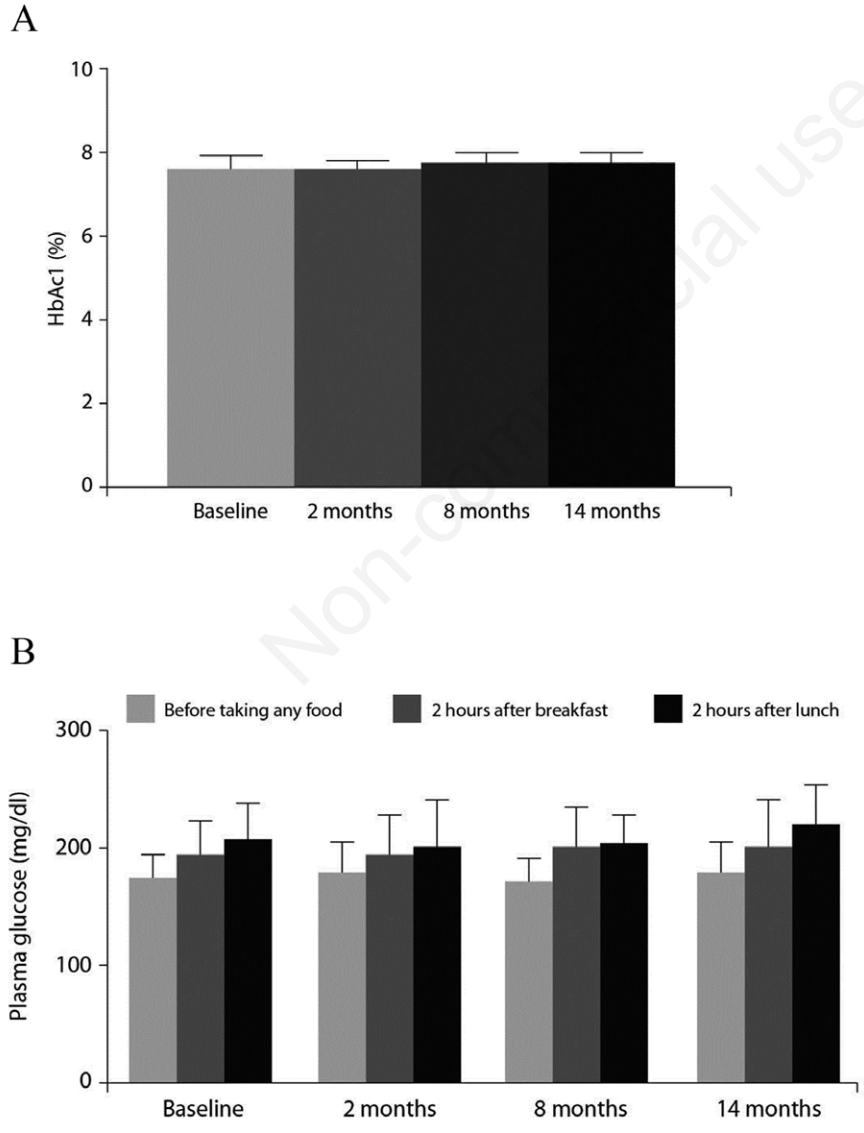

Figure 1. Glycemic control during treatment with linagliptin. A) Glycated hemoglobin (HbA1c) levels; B) plasma glucose levels.

treatment and significantly increased patient satisfaction with it.

Currently, there is a general lack of randomized clinical trials investigating glucose-lowering treatments in older diabetes patients with advanced CKD, like those included in this study. Due to their favorable safety profile, especially in terms of reduced hypoglycemia, DPP-4 inhibitors are probably the only oral glucose-lowering agents for which some evidence from dedicated randomized clinical trials in patients aged ≥65 years and/or with moderate to severe renal impairment has been published over the last few years.[3,19,32-40] One of these studies, a randomized, placebo-controlled trial in 133 patients with type 2 diabetes (HbA1c 7%-10%) and severe renal impairment (eGFR <30 mL/min per 1.73 m²) showed that adding linagliptin (5 mg/day) to existing background therapy resulted in a significantly greater reduction of HbA1c at 12 weeks[36] which was maintained at 1 year (P<0.0001 *vs* baseline). In linagliptin-treated patients the incidence of adverse events and severe hypoglycemia was similar to the placebo group. Of note, the effects on renal function were minimal with both placebo and linagliptin and numerically lower with linagliptin. A recent double-blind, randomized study, involving a 12-week placebo-controlled phase followed by a 40-week extension phase with glimepiride as active control, confirmed the efficacy and good tolerability of linagliptin 5 mg/day in type 2 diabetes patients with moderate to severe renal impairment (eGFR <60 mL/min per 1.73 m²).[40] After 52 weeks, mean reduction from baseline in HbA1c was –0.64% and –0.50% in the linagliptin and placebo/glimepiride groups, respectively. The incidence of adverse events, serious adverse events and adverse events leading to treatment discontinuation was numerically lower during treatment with linagliptin. Again renal function was not affected by 52 weeks of linagliptin treatment.

Consistent with previous findings from other studies, in our experience linagliptin was well tolerated for over 1 year. It is important to highlight that the treatment with linagliptin did not increase hypoglycemia in our population of patients with advanced CKD. It is well known that hypoglycemia is associated with significant morbidity and even mortality and is a major concern in the treatment of elderly diabetes patients who are particularly vulnerable to this complication.[41-43] The presence of advanced CKD further contributes to hypoglycemic risk. A study estimating the rates of emergency hospitalization for adverse drug events in US adults aged ≥65 years found that insulins and oral hypoglycemic agents were, respectively, the second and the fourth medication classes most commonly implicated in emergency hospitalizations.[44] A multi-centre

Italian retrospective analysis of the records from the emergency department due to hypoglycemia (n=3516) found, not surprisingly, that most events (94.0%) occurred in diabetes patients.[45] These patients were in treatment with insulin (49.8%), oral agents (31.4%), or a combination of both (15.1%). Notably, one-third of the patients required hospitalization. Diabetes treatment, older age and number of comorbidities were identified as risk factors for hospital admission. The mortality rate during hospitalization was 10%. Comparable results highlighting the burden of hypoglycemia to patients and the impact on resource use in Italy were reported also in a recent single-centre study.[46]

Suboptimal adherence to therapy, which may reduce treatment effectiveness, is another concern in the management of elderly patients with diabetes. The observed increase from 67% to 85% in the proportion of patients reporting high treatment adherence after the switch to linagliptin is relevant, considering that our study population consisted of difficult-to-treat patients. Several studies have shown an association between age, number and severity of complications, polypharmacy and frequency of daily dosing and poor compliance to antidiabetic treatment.[47,48] A significant association between compliance and long-term glycemic control has also been reported by several authors.[47,49] A recent analysis investigating whether self-reported medication adherence is predictive of future glycemic control found that each one-point increase in baseline Morisky total score (worsening of adherence) was associated with a 0.16% increase in HbA1c levels measured 6 months later.[50]

Patient-centered outcomes, including treatment satisfaction, are increasingly regarded as relevant measures for the evaluation of treatment effectiveness. The switch from injectable insulin to oral linagliptin was associated, perhaps not surprisingly, with a substantial (64.3%) and statistically significant improvement in the DTSQ score describing satisfaction with treatment. Other studies have reported lower satisfaction with the use of injectable antidiabetic therapy. According to the findings from a Dutch study investigating health-related quality of life (HRQOL) and treatment satisfaction (DTSQ) in type 2 diabetes patients, insulin therapy, obesity and complications were associated with lower HRQOL, regardless of age and sex.[51] A survey conducted among 630 diabetes patients also found that treatment satisfaction was lower in those taking insulin.[52] According to this survey, other factors independently associated with lower treatment satisfaction were female gender, diabetes complications and poor adherence.[52]

The findings of this study cannot be generalized because of several limitations, including the observational, open-label design, the small sample size and the absence of a specific clinical evaluation of frailty. However, the present study describes a group of difficult-to-treat, real-world patients who closely resemble those typically encountered in daily clinical practice. This study may therefore provide useful, practice-oriented information on the use of linagliptin, the experience with which is still limited in elderly diabetes patients with impaired renal function.

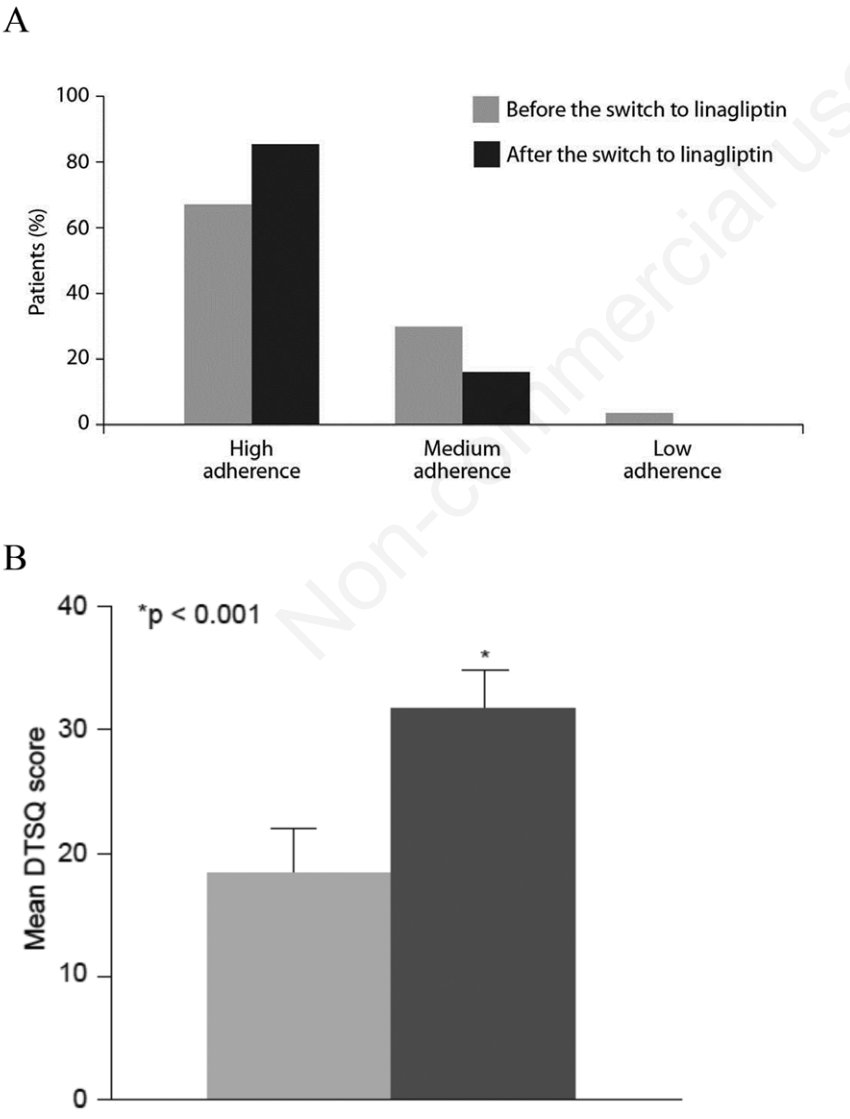

Figure 2. Adherence to treatment (A) and treatment satisfaction (B) before and after the switch to linagliptin. DTSQ, *diabetes treatment satisfaction questionnaire*.

Conclusions

This observational study evaluated the efficacy and safety of linagliptin 5 mg in elderly outpatients with type 2 diabetes and severe CKD previously treated with basal insulin. Linagliptin showed a favorable safety profile in this population. Compared with insulin, linagliptin achieved glycemic control similarly to insulin, with a lower risk of hypoglycemic events. Adherence to therapy and patient satisfaction, two key features of therapeutic success, were also improved by the switch to linagliptin. Therefore, linagliptin appears as a valid option for the individualized management of elderly patients with diabetes and advanced CKD. However well designed, long-term studies are needed to fully establish the role of linagliptin in the management of elderly diabetes patients with renal impairment.

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