Effect of Alogliptin, a DPP-4 Inhibitor, on Markers of Lipid Metabolism in Type 2 Diabetic Patients

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Abstract

Background: DPP-4 inhibitor has been shown to improve not only blood glucose levels but also dyslipidemia, but the effect remains controversial. Further, there are few reports regarding the influence on Apo B, Apo A-1 and Apo B/Apo A-1 in alogliptin.

Objective: Using the alogliptin, we focused on Apo B and Apo A-1, in addition to LDL-C, HDL-C and TG, and investigated the effect of alogliptin on markers predicting cardiovascular events, such as Apo B/Apo A-1 and LDL-C/Apo B.

Methods: This study was carried out with a single arm in an open label manner. 45 consecutive cases that could enroll between September 2011 and March 2012 were selected as the subjects for randomization. Alogliptin 25 mg/day was administered for eight weeks and non-fasting blood samples were collected 2-3 hours after breakfast, once at the beginning of the study and once eight weeks later, and changes in glucose and lipid metabolism markers were compared.

Results: Administration of alogliptin significantly reduced HbA1c levels and non-fasting blood glucose levels, and reduced LDL-C and non-fasting TG. Apo B was significantly reduced by alogliptin treatment but Apo A-1 was unchanged. The Apo B/Apo A-1 ratio was significantly decreased and the LDL-C/Apo B ratio significantly increased by alogliptin treatment. The change in the pre-administration Apo B/Apo A-1 ratio was positively correlated with body weight, TG, HbA1c, blood CPR and pooled urine CPR and negatively correlated with HDL-C

Conclusion: Administration of alogliptin in type 2 diabetic patients significantly improved levels of blood glucose, in addition to those of lipid metabolism markers such as LDL-C and non-fasting TG, as well as sensitive predictive markers for the onset risk of cardiovascular events, such as the Apo B/Apo A-1 ratio and the LDL-C/Apo B ratio. These results suggest that alogliptin could potentially suppress atherosclerosis and prevent cardiovascular events (UMIN 000011470).

Keywords

Alogliptin, Type 2 diabetes, Lipid metabolism, Apo B/Apo A-1, LDL/Apo B

Introduction

It is widely known that patients with diabetes have a higher risk of onset and mortality from cardiovascular events [1,2]. Meta-analysis of UKPDS has shown that the primary risk factor for cardiovascular (CV) events in diabetic patients is neither blood glucose levels nor HbA1c, but rather LDL-C [3]. Accordingly, an improvement not only in blood glucose levels but also in dyslipidemia is considered important for the prevention and avoidance of CV events.

In type 2 diabetes, increased influx of FFA into the liver due to insufficient insulin activity increases VLDL production, while reduced LPL activity increases VLDL, LDL-C, IDL and accelerates atherosclerosis [4]. A number of large-scale clinical studies have proven that statins decrease LDL-C and prevent CV events [5,6]. However, even a reduction in LDL-C leaves a residual risk, and hypertriglyceridemia, in particular, as well as postprandial TG elevation [7] and hyperHDLemia are risk factors.

Given the above data, current guidelines on diabetes treatment recommend appropriate control of hypercholesterolemia, hypertriglyceridemia and hyperHDLemia to prevent CV events [8]. In diabetic patients, abnormalities in both the quantity, and quality of LDL-C, such as increased small dense LDL-C and production of glycosylated LDL-C, are thought to increase the onset risk of CV events [9]. Electrophoresis is the standard method for measuring small dense LDL-C, but a complicated procedure. The LDL-C/Apo B ratio is used as an alternative, and it has been reported that small dense LDL is increased in cases in which the LDL-C/Apo B ratio is 1.2 or lower [10].

In Japan, DPP-4 inhibitors have been used as oral antidiabetic agents since 2011, and have also been shown to improve dyslipidemia. It has been reported that sitagliptin decreased TG and RLP-C without affecting levels of LDL-C and HDL-C [11]. Different from this result, another group showed it could decrease T-C and TG [12]. Thus, effects of sitagliptin toward dyslipidemia are still controversial. A meta-analysis of the effect on TC and TG has demonstrated differences in improvements in lipid metabolism markers and efficacy [13]. The non-fasting Apo B/Apo A-1 ratio has been proven
as a useful marker for predicting CV events [14]. According to the INTERHEART study, the non-fasting Apo B/Apo A-1 ratio may be a more sensitive predictive marker for acute myocardial infarction than either non-HDL-C or the T-C/HDL-C ratio. Additionally, the non-fasting Apo B/Apo A-1 ratio was not significantly influenced by age, gender or races. With regard to the influence of DPP-4 inhibitors on aprotinin, previous studies have examined decrease of postprandial chylomicon and Apo B48 levels with a focus on postprandial TG in sitagliptin [15] and in vildagliptin [16]. However, the measurement of both of Apo B, Apo A-1 is reported only in sitagliptin [15], and no report has studied the Apo B/Apo A-1 ratio with any DPP-4 inhibitors.

Thus, in this study, we highlighted Apo B and Apo A-1 and studied the effect of the DPP-4 inhibitors alogliptin [17,18] on Apo B and Apo A-1, in addition to lipid metabolism markers, and investigated the effect of alogliptin on markers predicting CV events, such as Apo B/Apo A-1 and LDL-C/Apo B.

Patients and Methods

Patients

Subjects were type 2 diabetic patients aged 20 years or older at our hospital that were taking oral antidiabetic agents and had HbA1c levels of 6.9% or higher for three months or longer. Exclusion criteria were: patients receiving insulin therapy; severe liver or renal dysfunction; patients with hypersensitivity to alogliptin; patients that had their hypoglycemic agents changed within three months; pregnant women or breast-feeding mothers; and excessive alcohol drinkers.

This study was carried out with a single arm in an open label manner. After informed consent was obtained from patients, 45 consecutive cases that could enroll between September 2011 and March 2012 were selected as the subjects for randomization. In the 45 cases, alogliptin 25 mg/day was administered for eight weeks and non-fasting blood samples were collected 2–3 hours after breakfast, once at the beginning of the study and once eight weeks later, and changes in height, body weight, blood pressure, glucose metabolism markers, and lipid metabolism markers were compared. Dietitians analyzed the ingredient of the breakfast by inquiring from 15 patients selected at random. The energy of their breakfast was 450Kcal, of which 32% was from fat. All the subjects take the same menu of the breakfast before study and eight weeks later. During this study, additional drugs that would influence blood pressure and lipid metabolism were not administered. Drug intake compliance was confirmed by interviewing patients at each visit to the hospital. Dietary and exercise therapy were unchanged before, during and after the study, and regular instructions were continued. We registered University hospital Medical Information Network (UMIN), and the registration number is 000011470.

Background information in the 45 cases that received alogliptin is shown in Table 1. Antidiabetic agents were administered as follows: sulfonylurea (SU), 27 cases; α-glucosidase inhibitors (α-GIs), 21; glinides, 14; biguanides (BGs), 18; and TZD, 11. Of these, all α-GIs and glinides were changed to alogliptin. Doses of BGs and TZD were unchanged and co-administered with alogliptin co-administered. With regard to SU, the dose was unchanged in 15 cases, reduced in 10, and increased, or another drug was necessary, in two. During administration, no adverse events occurred and administration was not discontinued in any case.

Biochemical analyses

Non-fasting blood samples were collected 2–3 hours after breakfast, once at the beginning of the study and once eight weeks later. Apo A-1 and Apo B were measured by immune nephelometry with BM8806. HbA1c levels were measured by HPLC with HLC-723G8. Measurements were converted to NGSP values with a conversion table recommended by the Japan Diabetes Society [19]. LDL-C and HDL-C were measured by the direct method, while TG was measured by the enzymatic colorimetric method with BM 2250.
also significantly reduced at -0.5% even in the reduced dose SU group (Figure 1b). There was no significant difference in the degree of reduction by alogliptin between obese patients with BMI ≥ 25 kg/m² and non-obese patients with BMI < 25 kg/m² (Figure 1c). Non-fasting blood glucose levels were significantly reduced by alogliptin from 164.6 ± 39.2 mg/dL (9.14 ± 2.18 mmol/L) to 141.2 ± 35.6 mg/dL (7.84 ± 1.98 mmol/L) (p < 0.001) (Table 2).

**Effect of alogliptin on lipid metabolism**

Alogliptin administration reduced LDL-C from 102.9 ± 19.7 mg/dL (2.66 ± 0.51 mmol/L) to 97.9 ± 22.5 mg/dL (2.53 ± 0.78 mmol/L) (p < 0.01). Alogliptin elevated HDL-C from 60.7 ± 19.3 mg/dL (1.57 ± 0.50 mmol/L) to 61.8 ± 18.3 mg/dL (1.60 ± 0.47 mmol/L), but the change was not significant. In contrast, the LDL-C/HDL-C ratio significantly decreased from 1.83 ± 0.60 to 1.68 ± 0.53 (p < 0.01). Moreover, non-fasting TG significantly decreased from 137.4 ± 93.9 mg/dL (1.55 ± 1.06 mmol/L) to 116.0 ± 71.1 mg/dL (1.31 ± 0.80 mmol/L) (p < 0.05) (Table 2).

The changes (amount and rate) of LDL-C, HDL-C, non-fasting TG were compared between obese (BMI ≥ 25 kg/m²) and non-obese patients (BMI < 25 kg/m²). The changes HDL-C in the obese patients were significantly more than the non-obese patients. There were no significant differences in the changes of LDL-C, HDL-C, and non-fasting TG between anti-diabetic agents (metformin, α-GIs, glinide, pioglitazone and sulfonylureas) combined with alogliptin.

**Effect of alogliptin on apoprotein**

Apo B was significantly reduced by alogliptin treatment from 91.0 ± 16.4 mg/dL (0.91 ± 0.16 g/L) to 85.0 ± 14.0 mg/dL (0.85 ± 0.14 g/L) (p < 0.01). Apo A-1 was unchanged in response to alogliptin. In contrast, the Apo B/Apo A-1 ratio was significantly decreased by alogliptin from 0.61 ± 0.15 to 0.57 ± 0.12 (p < 0.05), and the LDL-C/Apo B ratio significantly increased from 1.16 ± 0.11 to 1.20 ± 0.13 (p < 0.01) (Table 3).

The changes (amount and rate) of Apo B, Apo A-1, Apo B/Apo A-1, LDL/Apo B were compared between obese (BMI ≥ 25 kg/m²) and non-obese patients (BMI < 25 kg/m²). The changes Apo B in the obese patients were significantly more than the non-obese patients (Table 4).

There were no significant differences in the changes of Apo B, Apo A-1, Apo B/Apo A-1, LDL/Apo B between anti-diabetic agents (metformin, α-GIs, glinide, pioglitazone and sulfonylureas) combined with alogliptin.

The change in the pre-administration Apo B/Apo A-1 ratio was positively correlated with body weight, TG, HbA1c, blood CPR and pooled urine CPR and negatively correlated with HDL-C (Table 5). Changes in LDL and HbA1c before and after administration were positively correlated (Table 6).

**Table 3:** Alogliptin-induced changes in apoprotein and predictive markers for the onset risk of cardiovascular events

| Before administration | After administration | P value |
|-----------------------|----------------------|---------|
| ApoB 91.0 ± 16.4 mg/dL (0.91 ± 0.16 g/L) | 85.0 ± 14.0 mg/dL (0.85 ± 0.14 g/L) | p < 0.01 |
| ApoA-1 153.1 ± 27.4 mg/dL (1.53 ± 0.27 g/L) | 153.9 ± 28.1 mg/dL (1.54 ± 0.28 g/L) | NS |
| ApoB/ApoA-1 0.61 ± 0.15 | 0.57 ± 0.12 | p < 0.05 |
| LDL/ApoB 1.16 ± 0.11 | 1.20 ± 0.13 | p < 0.01 |

**Table 4:** Changes in lipid metabolism markers by alogliptin between patients with BMI < 25 kg/m² and BMI ≥ 25 kg/m². Data are means ± SD. * p < 0.05 between BMI < 25 kg/m² and BMI ≥ 25 kg/m²

| LDL (mg/dL) | HDL (mg/dL) | TG (mg/dL) | Apo B (mg/dL) | Apo B/A-1 (mg/dL) | LDL /Apo B |
|-------------|-------------|-----------|--------------|------------------|-----------|
| BMI<25 | BMI≥25 | BMI<25 | BMI≥25 | BMI<25 | BMI≥25 | BMI<25 | BMI≥25 | BMI<25 | BMI≥25 | BMI<25 | BMI≥25 |
| 25 | 103.1 ± 17.0 | 96.0 ± 21.1 | -7.16 ± 13.8 | -6.93 ± 14.3 | |
| 20 | 102.7 ± 23.2 | 100.4 ± 21.1 | -2.30 ± 9.10 | -2.14 ± 8.49 | |
| 25 | 65.5 ± 20.7 | 64.6 ± 19.9 | -0.88 ± 6.46 | -0.46 ± 10.4 | |
| 20 | 54.7 ± 16.0 | 56.3 ± 15.9 | 3.60 ± 4.78 | 7.24 ± 9.07 | |
| 25 | 135.9 ± 94.0 | 117.6 ± 81.1 | -18.4 ± 55.4 | -8.90 ± 32.3 | |
| 20 | 139.2 ± 96.2 | 114.1 ± 58.3 | -25.1 ± 79.3 | -7.75 ± 30.6 | |
| 25 | 88.1 ± 20.7 | 82.2 ± 15.2 | -5.9 ± 8.92 | -5.43 ± 8.49 | |
| 20 | 156.6 ± 33.8 | 151.8 ± 33.9 | -4.73 ± 11.0 | -3.03 ± 6.36 | |
| 25 | 149.4 ± 19.3 | 156.2 ± 21.5 | 6.80 ± 10.1 | 4.70 ± 6.97 | |
| 20 | 0.621 ± 0.133 | 0.595 ± 0.114 | -0.026 ± 0.06 | -3.27 ± 8.98 | |
| 25 | 0.600 ± 0.179 | 0.537 ± 0.135 | -0.064 ± 0.061 | -9.54 ± 8.03 | |
| 20 | 1.14 ± 0.13 | 1.19 ± 0.17 | 0.048 ± 0.069 | 4.79 ± 6.94 | |
| 25 | 1.18 ± 0.086 | 1.21 ± 0.092 | 0.094 ± 0.20 | 3.02 ± 5.29 | |
Table 6: Correlations between change in Apo B/Apo A-1 and clinical parameters (values prior to treatment)

| Parameter          | Correlation coefficient (R) | Contribution rate (R²) | P value |
|--------------------|----------------------------|------------------------|---------|
| Age                | -0.161                     | 0.026                  | p<0.05  |
| Body weight        | 0.470                      | 0.221                  | p<0.05  |
| LDL-C              | 0.296                      | 0.088                  | ns      |
| HDL-C              | -0.558                     | 0.312                  | p<0.01  |
| TG                 | 0.541                      | 0.292                  | p<0.05  |
| Hba1c              | 0.482                      | 0.232                  | p<0.05  |
| Glu                | 0.224                      | 0.050                  | ns      |
| Blood CPR          | 0.714                      | 0.510                  | p<0.001 |
| Pooled urine CPR   | 0.532                      | 0.283                  | p<0.05  |

Effect of alogliptin on blood pressure

Alogliptin effected reductions in SBP (125.2 ± 12.8mmHg to 123.6 ± 15.8mmHg) and DBP (67.6 ± 9.0mmHg to 65.9 ± 10.7mmHg) but neither change was significant. However, since blood pressure guidelines recommend a SBP<130mmHg, only 18 cases with abnormal SBP (defined as 130mmHg or higher) were examined, and in these cases, SBP was significantly reduced by alogliptin treatment from 137.9 ± 5.5mmHg to 128.0 ± 15.6mmHg (p<0.01).

Discussion

We have shown here for the first time that administration of alogliptin over an eight week period at 25 mg/day improved not only blood glucose levels, but also blood levels of LDL-C and non-fasting TG. Furthermore, by improving Apo B levels, alogliptin significantly reduced the Apo B/Apo A-1 ratio, a reliable predictive marker for the onset risk of acute myocardial infarction. It also significantly increased the LDL-C/Apo B ratio, which correlated with small dense LDL, which would be expected to reduce the proportion of small dense LDL.

It has been reported that DPP-4 inhibitors could decrease fasting serum TG. Furthermore, inhibition by alogliptin of TG, Apo B48 and Apo B100 elevation for up to 8 h after meals, has been attributed to improvements in chylomicron TG derived from foods and TG contained in VLDL from the liver [20]. Moreover, it is known that GLP-1 inhibits both TG absorption from the intestine and production of Apo B48 in mice [21]. In human, reduction of Apo B and Apo B48 is reported in sitagliptin [15] and reduction of Apo B is reported in vildagliptin [22]. The reduction in non-fasting TG and Apo B by alogliptin in this study is consistent with the previous reports of TG reduction by GLP-1. In this context, it can be speculated that continuous suppression by alogliptin of the enzymatic activity of DPP-4 results in chronically elevated GLP-1 levels, and suppression of postprandial TG elevation.

In many clinical studies, it has been reported that treatment of LDL-C could prevent CV events. The effect of DPP-4 inhibitors on LDL-C is still controversial. Sitagliptin [12,15] and vildagliptin [23] have been shown to reduce TG, but not LDL-C. In addition, a meta-analysis of the effect of DPP-4 inhibitors on T-C showed that vildagliptin and alogliptin decreased T-C in contrast to sitagliptin [13], suggesting the possibility that distinct DPP-4 inhibitors have different effects on cholesterol metabolism. In this study, alogliptin administration reduced postprandial LDL-C.

According to the INTERHEART study, non-fasting Apo B and Apo B/Apo A-1 are important predictive markers for the onset risk of acute myocardial infarction [14]. In particular, the Apo B/Apo A-1 ratio corresponded to the highest odds ratio among predictive markers and it has been considered a marker that would sensitively predict acute myocardial infarction independent of races, gender, age or diet. In this study eight weeks of alogliptin administration significantly reduced Apo B and the Apo B/Apo A-1 ratio. Since the possibility that DPP4 inhibitors may prevent CV events has attracted attention, the results of this study suggest the potential of this drug for suppressing CV events. When we examined factors that influenced the improvement in the Apo B/Apo A-1 ratio by alogliptin, we found significant positive correlations with body weight, TG, Hba1c, and blood and pooled urine CPR prior to administration, and a significant negative correlation with HDL-C.

In metabolic syndrome cases where body weight and TG are increased and intrinsic insulin secretion is maintained or is slightly increased due to insulin resistance, an improvement in Apo B/Apo A-1 is unusual. CETP activity is increased under insulin resistance, and excessive TG levels increase cholesterol transfer from HDL-C to VLDL, and reduce HDL-C. Therefore, alogliptin was more effective in cases where HDL-C levels were reduced. In this study, by comparison of all cases, Apo A-1 and HDL-C did not have the significant difference with about administration of alogliptin. However, when they divided it into the obesity patient and the non-obesity patient, HDL-C and Apo A-1 were significantly more in the obesity patients compared with the non-obesity patient. Administration of alogliptin to the obesity patient may contribute to anti-atherosclerosis by increase HDL-C and Apo A-1.

In the context of DPP-4 inhibitors, the degree of Hba1c reduction has been shown to be larger in cases with higher Hba1c levels before administration [24] and, similarly, we observed an improvement in the Apo B/Apo A-1 ratio. In response to postprandial hyperglycemia, DPP-4 inhibitors, increase GLP-1 and insulin secretion and suppress glucagon secretion. In cases with higher remaining capability of insulin secretion, reactive insulin secretion and suppression of glucagon secretion were more pronounced and both blood glucose levels and lipid metabolism were improved.

We have shown that improvement in Apo B/Apo A-1 has a significant positive correlation with change in LDL-C and Hba1c before and after the administration of alogliptin. A positive correlation with Hba1c suggests that the improvement in glycemic control by alogliptin contributed to an improvement in the Apo B/A-1 ratio. In this study, postprandial blood CPR was not significantly different before and after the administration, which we speculate is related to reduced insulin resistance by suppression of glucagon secretion.

In animal experiments, GLP-1 signal activation has been shown to suppress cholesterol absorption from the intestine [21] and GLP-1 analog administration is known to upregulate LDL receptor expression in the liver [25], suggesting a possible mechanism of not only LDL-C reduction via insulin but also direct reduction of GLP-1. In the context of DPP-4 inhibitors, the degree of Hba1c reduction has been shown to be larger in cases with higher Hba1c levels before administration [24] and, similarly, we observed an improvement in the Apo B/Apo A-1 ratio. In response to postprandial hyperglycemia, DPP-4 inhibitors, increase GLP-1 and insulin secretion and suppress glucagon secretion. In cases with higher remaining capability of insulin secretion, reactive insulin secretion and suppression of glucagon secretion were more pronounced and both blood glucose levels and lipid metabolism were improved.

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analysis of phase II and phase III clinical trials in the U.S. which has shown that alogliptin reduced the major adverse CV events [31]. In EXAMINE trial, reported in 2013, alogliptin didn’t demonstrate the superior effects on the prevention of death from CV causes, nonfatal myocardial infarction or nonfatal stroke in patients with type 2 diabetes with a recent acute coronary syndrome [32]. It is possible that the observation period was too short, and the subjects were too little for evaluation of the effect on prevention of CV events. In UKPDS trial, observation more than 10 years was necessary so that significant difference appeared by CV events. Therefore, the EXAMINE study may prove the beneficial effects of alogliptin if it has a longer observation period. In addition, it may influence it that the patients with very high risk for CVD were subjected. In the view of alogliptin effect, improved glucose and lipid metabolism and direct action of GLP-1 for cardiac function may be beneficial for CVD. However the risk reduction in the diabetic patients with CVD is difficult and earlier intervention should be needed.

Conclusions

Alogliptin administration in type 2 diabetic patients significantly improved levels of blood glucose, in addition to those of lipid metabolism markers such as LDL-C and non-fasting TG, as well as sensitive predictive markers for the onset risk of CV events, such as the Apo B/Apo A-1 ratio and the LDL-C/Apo B ratio. These results suggest the possibility that alogliptin could potentially suppress atherosclerosis and prevent CV events.

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