Analyzing the Factors Contributing to Withdrawal from Insulin Therapy Following Additional Administration of Alogliptin: Retrospective Study after Removing Glucotoxicity with Insulin

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ABSTRACT: We attempted to examine whether withdrawal from insulin therapy is or is not possible with administration of additional alogliptin and identify the contributing factors. The subjects were 43 adult patients with type 2 diabetes undergoing insulin therapy after admission. After glucotoxicity was removed, 25 mg alogliptin was additionally administered. Insulin was reduced by 15.6 ± 13.0 units (mean ± SD), and 17 patients (39.5%) completely withdrew from insulin therapy. Several factors were compared between the two groups of patients: those who could withdraw from insulin therapy and those who could not. The former group showed lower HbA1c levels on admission, a lower insulin dose before adding alogliptin, lower injection frequencies, and longer treatment histories prior to admission. Logistic regression analysis showed that lower insulin dose contributed significantly to withdrawal. These results suggest that a lower insulin dose is the best predictor for withdrawal from insulin therapy after adding alogliptin.

KEYWORDS: alogliptin, insulin therapy, type 2 diabetes

Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitor is a drug that indirectly accelerates insulin secretion by increasing the gastric inhibitory polypeptide and glucagon-like peptide-1 concentrations in the blood. This drug plays an important role in the current treatment of diabetes because it offers two major advantages: (1) when used as a single drug, it has fewer adverse effects such as serious hypoglycemia and body weight gain; and (2) pancreatic beta cell exhaustion is not caused. Glycated hemoglobin (HbA1c) may be also improved by adding DPP-4 inhibitor when the effects of conventional hypoglycemic agents are insufficient. For example, the HbA1c level decreased by ~0.6% with biguanide (BG), by 0.4%–0.6% with sulfonylurea (SU), by 0.6%–0.9% with thiazolidine (TZD), and by ~0.9% with alpha glucosidase inhibitor (αGI). Insulin is the most effective glucose-lowering agent, but there have been multiple reports indicating that HbA1c was improved as a result of additional administration of DPP-4 inhibitor to patients who were insufficiently controlled even with insulin therapy. It was reported that the HbA1c level decreased by approximately 0.6%, for example, by 0.6%–0.9% with alogliptin, by 0.5% with vildagliptin, by 0.6% with linagliptin, and by 0.6% with sitagliptin.

The occurrence ratio of hypoglycemia, a potentially serious complication when a diabetes drug is administered, varies amongst the available drugs; according to published reports, in case of vildagliptin, it was lower than that of a placebo. In case of alogliptin and linagliptin, the occurrence ratio was the same as a placebo. The occurrence ratio for sitagliptin was found to be higher than for a placebo. If blood sugar improves to a point such that hypoglycemia could be caused, insulin units can be reduced to prevent the risk of hypoglycemia, and some patients may withdraw from insulin therapy, freeing them from complicated self-injections and reducing their financial burden. However, there are very few clinical studies on how much insulin units can be reduced by the concomitant use of these drugs, if withdrawal is possible, and what effects may be expected on the patient. Therefore, in this study, the early effects upon the concomitant use of DPP-4 inhibitor in patients undergoing insulin therapy and the clinical factors involved in predicting withdrawal from insulin therapy were investigated.

Subjects and Methods

The subjects were selected from among type 2 diabetes adult patients admitted to Fukuyama City Hospital between...
October 2010 and June 2013. A flowchart of the study selection process is shown in Figure 1. Of the 451 patients, we extracted 80 patients who had been treated with alogliptin for the first time during their period of hospitalization. Among these subjects, we excluded 27 patients who were not treated with insulin to control their blood sugar levels at the beginning of their hospital admission because they had premeal blood sugar levels of ~170 mg/dL or below. We also excluded 10 patients who were experiencing renal dysfunction complications as indicated by findings of creatinine [Cr] ≥1.0 or estimated glomerular filtration rate [eGFR] ≤50 or who were concomitantly using steroids, had cancer, had serious liver damage, or whose medical records were ambiguous. The presence of other vascular complications was not considered.

The 43 subjects were administered alogliptin (Takeda Pharmaceutical Company Ltd.) for the purpose of reduction of insulin units or withdrawal from insulin therapy after their fasting blood sugar levels improved to ~130 mg/dL by increasing insulin, and they were analyzed retrospectively. The dosage was 25 mg taken once in the morning, which is the recommended dose for patients without renal impairment in Japan. This study was not in conflict with principles expressed in the Declaration of Helsinki.

The 43 subjects comprised 28 men and 15 women, aged 63.1 ± 10.2 years. Further characteristics of the group are listed in Table 1. The type and dosage of insulin drugs used during hospitalization are listed in Table 2. A total of 12 patients concomitantly taking oral hypoglycemic agents other than DPP-4 inhibitor continued to take the same medication. The breakdown of their oral hypoglycemic agents is listed in Table 3.

In order to extract background factors involved in withdrawal, a comparison was made between the two groups with regard to age, body mass index (BMI), disease duration, treatment history of diabetes prior to admission, the required daily insulin units immediately prior to concomitant use of DPP-4 inhibitor, the number of injections per day, HbA1c on hospital admission, the treatment history prior to admission, the number of injections per day, and the required daily insulin units. The background factors were compared between the WG group and the NWG group, significant differences were observed in the HbA1c level upon hospital admission, the treatment history prior to admission, the number of injections per day, the required daily insulin units, and the reduced insulin units.

| Table 1. Clinical characteristics of the patients. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| N (M/F) | 43 (28/15) | 17 (11/6) | 26 (17/9) | 0.96* |
| Age (y) | 63.1 ± 10.2 | 65.8 ± 11.9 | 61.4 ± 8.8 | 0.17 |
| BMI (kg/m²) | 23.8 ± 4.5 | 24.1 ± 4.1 | 23.7 ± 4.8 | 0.79 |
| Disease duration <10 y:≥10 y | 22:14 (7; unknown) | 9:5 (3; unknown) | 12.1 ± 11.0 | 0.03 |
| HbA1c (%) | 11.0 ± 2.4 | 9.9 ± 2.8 | 11.7 ± 1.9 | 0.02 |
| fCPI | 0.6 ± 0.3 | 0.74 ± 0.37 | 0.58 ± 0.33 | 0.18 |
| Treatment history prior to admission | 15 (34.9%) | 9 (52.9%) | 6 (23.1%) | 0.045*** |
| Number of injections per day | 3.5 ± 0.8 | 3.0 ± 0.9 | 3.8 ± 0.5 | 0.001 |
| Required daily insulin units (unit/kg) | 30.4 ± 18.7 (0.49 ± 0.27) | 21.0 ± 14.2 (0.33 ± 0.21) | 36.5 ± 18.9 (0.58 ± 0.27) | 0.006 (0.002) |
| Reduced insulin units | 15.6 ± 13.0 | 21.0 ± 14.1 | 12.1 ± 11.0 | 0.03 |

Notes: Data are mean ± SD or n. χ² value *0.002, **2.4, *4.0. When the background factors were compared between the WG group and the NWG group, significant differences were observed in the HbA1c level upon hospital admission, the treatment history prior to admission, the number of injections per day, the required daily insulin units, and the reduced insulin units.
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admission (upon introduction of insulin), and fasting C-peptide index (iCPI), which is an index of the insulin secretion capacity, on admission (fasting C-peptide [ng/mL] × 100/fasting blood sugar levels [mg/dL]). The blood samples were collected before breakfast, after a fasting period of nine hours or longer. The HbA1c levels were measured using a Latex Agglutination Reaction Method kit (Kyowa Medex Co., Ltd.), with a normal range considered to be 4.6%–6.2%. The C-peptide levels were measured using a Chemiluminescent Immunoassay kit (Siemens Healthcare Diagnostics), with a normal range considered to be 0.74–3.48 ng/mL.

Moreover, the contribution of the aforementioned factors to insulin withdrawal and the difference between both groups were investigated with logistic regression analysis, with the odds ratio after adjustment for other factors calculated with a 95% confidence interval (CI). The measured values were presented as the average ± SD, and differences in continuous variables were tested using the Student’s t-test. Differences in categorical variables were tested using the χ² test, and a P value of <0.05 was regarded as indicating a significant difference. Statistical significance was analyzed using JMP Version 10.

**Results**

It was possible to decrease the insulin requirements of all 43 cases from 30.4 ± 18.7 units to 14.8 ± 15.7 units, a difference of 15.6 ± 13.0 units (maximum of 53 units and minimum of 0 units). There were 17 cases (39.5%, men/women: 11/6) in the WG and 26 cases (60.5%, men/women: 17/9) in the NWG. Patient background information for each group is provided in Table 1.

In these groups, there was no significant difference in sex, age, BMI, and disease duration (<10 years/≥10 years), but HbA1c on admission to hospital was lower in the WG (95% CI 5.2–15.3, P = 0.02). No difference was observed in fCPI between the two groups (95% CI 0.17–1.79, P = 0.18).

Regarding the treatment history prior to admission, in the NWG, there were more patients who had no treatment history prior to admission (P = 0.045). The required daily insulin units immediately prior to concomitant use of DPP-4 inhibitor was 21.0 ± 14.2 units for WG and 36.5 ± 18.9 units for NWG (95% CI 3–83, P = 0.006), with the units adjusted for weight being 0.33 ± 0.21 units/kg and 0.58 ± 0.27 units/kg (95% CI 0.04–1.12, P = 0.002), respectively, and the number of injections per day being 3.0 ± 0.9 times and 3.8 ± 0.5 times (95% CI 1.0–4.0, P = 0.026), both of which were lower in the WG. In the WG, the insulin was ultimately reduced by 21.0 ± 14.1 units, which was twofold greater than the NWG group (95% CI 0–53, P = 0.03).

Between the two groups, differences in the required insulin units and the HbA1c level upon admission were observed, so the effects of these differences on insulin withdrawal were examined using a logistic regression analysis. Patients were divided into three groups based on their required insulin units adjusted for body weight: a high-dose group (≥0.5 units/kg, n = 16), a medium-dose group (0.357–0.5 units/kg, n = 13), and a low-dose group (0.04–0.356 units/kg, n = 14). The crude odds ratios and the adjusted odds ratios of the low-dose and the

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**Table 2. The type and the number of injections per day of insulin drugs of patients.**

| ULTRA-RAPID | REGULAR | NPH | ULTRA-LONG ACTING | PREMIXED | n |
|-------------|---------|-----|------------------|----------|---|
| 4 times a day (n = 27) | 3 | 1 | 3 | 13 |
| 3 times a day (n = 10) | 2 | 1 | 3 | 6 |
| Twice a day (n = 5) | 2 | 2 | 2 | 1 |
| Once a day (n = 10) | 1 | | | 1 |

**Table 3. Oral hypoglycemic agents that were used concomitant with insulin therapy.**

| ORAL HYPOGLYCEMIC AGENTS | n |
|---------------------------|---|
| SU                        | 1 |
| SU + αGI                 | 1 |
| SU + BG                  | 1 |
| SU + αGI + TZD           | 2 |
| Glinide + αGI + BG + TZD | 1 |
| BG                       | 3 |
| αGI + TZD                | 1 |
| DPP-4i                   | 2 |
| None                     | 31 |

**Abbreviations:** SU, sulfonylurea; BG, biguanide; αGI, alpha glucosidase inhibitor; TZD, thiazolidine; DPP-4i, DPP-4 inhibitor (stopped after commencement of insulin administration).
medium-dose groups, compared with those of the high-dose group, were calculated to assess the effect on insulin withdrawal (Table 4). The factors used to calculate the adjusted odds ratios were age, sex, disease duration, BMI, HbA1c upon admission, fCPI upon admission, and treatment history of diabetes prior to admission. Although there were no significant differences in the medium-dose group in either analyses, the low-dose group experienced a significantly higher rate of withdrawal from insulin therapy (Fig. 2A).

In the same manner, the patients were divided into the following three groups based on their HbA1c level upon admission to the hospital: a high-level group (≥12.1%, n = 15), a medium-level group (9.9%–12.0%, n = 14), and a low-level group (5.2%–9.8%, n = 14). The crude odds ratios and the adjusted odds ratios of the low-level and the medium-level groups, compared with the high-level group, were calculated to assess the effect on insulin withdrawal. The factors used to calculate the adjusted odds ratios were age, sex, disease duration, BMI, the number of insulin units adjusted for body weight, fCPI upon admission, and treatment history of diabetes prior to admission. No significant differences in the HbA1c level were seen among the groups (Fig. 2B).

**Table 4. Multiple logistic regression analysis of withdrawal from insulin therapy.**

| VARIABLES | CRUDE ODDS RATIO (95% CI) | P-VALUE | ADJUSTED ODDS RATIO (95% CI) | P-VALUE |
|-----------|---------------------------|---------|-------------------------------|---------|
| HbA1c (L) | 2.96 (0.80–11.6)          | 0.1     | 1.4 (0.11–18.3)               | 0.78    |
| HbA1c (M) | 1.22 (0.33–4.5)           | 0.76    | 6.0 (0.35–220.0)              | 0.22    |
| HbA1c (H) | 1                         |         | 1                             |         |
| Insulin dose (L) | 7.9 (1.99–36.9) | 0.003 | 40.5 (3.64–1404.5) | 0.0014 |
| Insulin dose (M) | 0.58 (0.13–2.23) | 0.43  | 2.2 (0.09–83.8)               | 0.6     |
| Insulin dose (H) | 1                         |         | 1                             |         |

Notes: HbA1c (L): a low-level group (5.2%–9.8%, n = 14), (M): a medium-level group (9.9%–12.0%, n = 14), and (H): a high level group (≥12.1%, n = 15). Insulin dose (L): a low-dose group (0.04–0.356 units/kg, n = 14), (M): a medium-dose group (0.357–0.5 units/kg, n = 13), and (H): high dose (≥0.5 units/kg, n = 16).

**Discussion**

Our study revealed that insulin may be reduced by 15.6 units on average with additional administration of DPP-4 inhibitor, and a withdrawal rate of 39.5% was also achieved. In conventional studies on additional administration of DPP-4 inhibitor to insulin therapy, the target was to maximize improvement of the HbA1c levels in poorly controlled patients, rather than reducing insulin or withdrawal from insulin therapy. Paresh and Samrat reported that insulin was reduced by 10 units on average by administrating 50 mg vildagliptin to Indian patients with HbA1c of ≥7% for 12 weeks. However, the dosage of vildagliptin was different from the usual dosage in Japan, and it was administered to inadequately controlled patients; thus, the number of units could only be used as a reference. Therefore, this report provides valuable data resulting from a study on the normal dose of DPP-4 inhibitor in Japanese people for the first time.

Factors for predicting whether withdrawal from insulin therapy is possible or not were reported by Kanda et al in 2004, which were before DPP-4 inhibitor was placed in the market. According to the report, when SU, nateglinide, and/or metformin were used as the principal oral hypoglycemic agent, the predicting factors for withdrawal from insulin therapy within one year from its introduction were said to be small insulin dose at withdrawal, short diabetes duration, and low HbA1c level at withdrawal.

Our study showed similar results in cases where the required daily insulin units immediately prior to concomitant use of DPP-4 inhibitor were small; however, no significant difference was observed with regard to disease duration, and the logistic regression analysis indicated no significant
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Differences based on HbA1c levels. The surmised reasons for the differences are as follows. Regarding disease duration, in many cases, it was vague or unclear when our patients were diagnosed with diabetes, so they had to be roughly divided into two groups with 10 years as the boundary. Regarding HbA1c, in our study, the period from the start of insulin administration to the start of concomitant use of DPP-4 inhibitor was very short, at one to two weeks; and the HbA1c levels on admission to the hospital were used for the analysis; owing to this, it is believed that the condition after the removal of glucotoxicity and resistance to insulin by insulin therapy was not reflected.

Moreover, in our study, the ratio of patients with no treatment history of diabetes prior to admission was high in the NWG, with a slight significant difference observed. This might indicate that patients with no treatment history had a tendency to have high HbA1c and require more insulin, making them difficult to withdraw from insulin therapy.

A significant difference was observed in insulin requirements immediately prior to the concomitant use of DPP-4 inhibitor, in the same manner as the study by Kanda et al. The difference became clearer when this was adjusted for body weight; for WG, the average was 0.3 units/kg, and for the NWG, it was 0.6 units/kg or twofold greater. The logistic regression analysis clarified that having a small number of insulin units (~0.356 units/kg) was strongly related to the withdrawal from insulin therapy when alogliptin was added.

The injection frequency was slightly lower and the more number of insulin units was reduced in WG (than NWG). That was first surmised to be because of differences in the secretional capacity of insulin; however, no difference in iCPI levels was observed between the groups. Ahren et al reported that immunoreactive insulin (IRI) levels in the blood did not increase even when vildagliptin was administered and that glucagon secretion was inhibited. Therefore, the insulin reduction effect in this study may have been because of glucagon secretion inhibition and not insulin secretion stimulating effects of DPP-4 inhibitor. However, some reports mention that the postprandial CPI level is more useful than the premeal CPI level to determine whether or not insulin therapy is necessary, and perhaps, the results would have been different if the postprandial CPI level was measured.

This study had several limitations, as follows. (1) This study was an observational study and was performed based on a retrospective chart search. We did not collect appropriate control patients, and comparisons with patients who did not receive alogliptin could not be performed. (2) The sample size was very small, since patients were excluded from the study if they had an unstable medical condition or complication that affected blood control. Therefore, whether the same result would be obtained with a larger sample size is uncertain. (3) The start of the concomitant use of the DPP-4 inhibitor was very early (an average of 10 days after the start of insulin therapy); therefore, the effects of the improvement in insulin resistance and glucotoxicity may have contributed to the reduction in insulin units following the administration of the DPP-4 inhibitor. The actual contribution level is unclear, since control patients were absent. To eliminate these effects, the administration of a DPP-4 inhibitor should have been withheld until the target blood sugar level was reached and the required insulin units had stabilized for a set period of time after the start of insulin therapy. (4) The observation periods after insulin withdrawal were relatively short. Some of the present results might have changed if a longer observation period had been performed. Ideally, the study should have been performed in a controlled environment in which the patients’ caloric intake was fixed. However, such a design is unrealistic because of the cost and time it would demand. Overall, we conclude that the concomitant use of a DPP-4 inhibitor is worthwhile when the required insulin units are small and an attempt to withdraw from insulin therapy is being made.

Conclusion

When the required insulin units are small and blood sugar is adequately controlled with insulin therapy, it is worth attempting to use DPP-4 inhibitor to withdraw from insulin therapy.

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Author Contributions

Contributed to the study concept, data collection, statistical analysis, and writing of the manuscript: HH. Contributed to supervision of the statistical analysis, methods and results, and review and editing of the manuscript: KN and MN. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Seino Y, Yabe D. Alogliptin benzoate for the treatment of type 2 diabetes. Expert Opin Pharmacother. 2014;15:851–863.
2. Seino Y, Fujita T, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. Curr Med Res Opin. 2011;27:1781–1792.
3. Scherbaum WA, Schweizer A, Mari A, et al. Evidence that vildagliptin attenuates deterioration of glycemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycemia. Diabtoes Metab. 2008;10:1114–1124.
4. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007;132(6):2131–2157.
5. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q. Alogliptin Study 008 Group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2008;63:46–55.
6. Seino Y, Miyata Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomised, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Metab. 2012;14:927–936.
7. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q. Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Metab. 2009;11:167–176.
8. Seino Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to sulfonylurea in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. J Diabetes Invest. 2012;3:517–525.

9. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009;25:2361–2371.

10. Kaku K, Irayasu T, Hiroi S, Hirayama M, Seino Y. Efficacy and safety of alogliptin added to pioglitazone in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label long-term extension study. Diabetes Obes Metab. 2011;13:1028–1035.

11. Seino Y, Fujita T, Hiroi S, Hirayama M, Kaku K. Alogliptin plus voglibose in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label long-term extension study. Curr Med Res Opin. 2011;27(suppl 3):21–29.

12. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA1c without causing weight gain or increased hypoglycaemia. Diabetes Obes Metab. 2009;11:1145–1152.

13. Kaku K, Mori M, Kanoo T, Katou M, Seino Y. Efficacy and safety of alogliptin added to insulin in Japanese patients with type 2 diabetes: a randomized, double-blind, 12-week, placebo-controlled trial followed by an open-label, long-term extension phase. Expert Opin Pharmacother. 2014;15(15):1–10.

14. Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S. Addition of vildagliptin to insulin improves glycemic control in type 2 diabetes. Diabetologia. 2007;50:1148–1155.

15. Yki-Järvinen H, Rosenstock J, Durán-Garcia S, et al. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study. Diabetes Care. 2013;36:3875–3881.

16. Vilsbøll T, Rosenstock J, Yki-Järvinen H, et al. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:167–177.

17. Paresh V, Samrat S. Evaluation of vildagliptin and fixed dose combination of vildagliptin and metformin on glycemic control and insulin dose over 3 months in patients with type 2 diabetes mellitus. Indian J Endocrinol Metab. 2012;16(suppl 1): S110–S113.

18. Kanda Y, Yamada K, Harada Y, et al. Clinical parameters for predicting possibility of insulin therapy withdrawal in patients with type 2 diabetes mellitus. Jpn J Endocrinol Metab. 2014;94(4):271–275.

19. Ahrén B, Schweizer A, Dejager S, et al. Vildagliptin enhances islet responsiveness to both hyper- and hypoglycaemia in patients with type 2 diabetes. J Clin Endocrinol Metab. 2009;94(4):1236–1243.

20. Saisho Y, Kou K, Tanaka K, et al. Postprandial serum C-peptide to plasma glucose ratio as a predictor of subsequent insulin treatment in patients with type 2 diabetes. Endocr J. 2011;58(4):315–322.