International Journal of Diabetes & Clinical Diagnosis
Short Communication Open Access

Effects of Combination Therapy with Liraglutide and Insulin Glargine as the Initial Treatment for Hyperglycemic Patients with Type 2 Diabetes: An Observational Study

Kotaro Kurasaki, Ikue Kigawa, Emi Sohara and Kumiko Hamano*
Department of Diabetes and Endocrinology, Kanto Rosai Hospital, 1-1 Kizukisumiyoshi, Nakahara, Kawasaki, Kanagawa 211-8510, Japan

Abstract

Background: Hyperglycemia in type 2 diabetes causes glucotoxicity, which can be treated with intensive insulin therapy. However, this treatment can lead to weight gain and hypoglycemia. The present study investigated the efficacy and safety of combination therapy with liraglutide and insulin glargine as the initial treatment for patients with moderate or severe hyperglycemia.

Methods: Changes in clinical indexes such as glycated hemoglobin (HbA1c) and body mass index (BMI) were retrospectively investigated in 20 patients under combination therapy with liraglutide and insulin glargine and 10 patients treated with intensive insulin therapy.

Results: Combination therapy with liraglutide and insulin glargine significantly improved HbA1c and BMI at 3 months compared with baseline. However, BMI was not improved in patients treated with intensive insulin therapy. Severe hypoglycemia was not observed in the combination therapy group during the observation period, and no patients required switching because of gastrointestinal symptoms.

Conclusion: Combination therapy with liraglutide and insulin glargine demonstrated a superior glucose-lowering effect, safety, and convenience without increasing body weight in poorly controlled patients with type 2 diabetes under hyperglycemic conditions. These results suggest that combination therapy could be considered an alternative to intensive insulin therapy.

Publication History:

Received: September 06, 2016
Accepted: December 13, 2016
Published: December 15, 2016

Keywords:

Glucotoxicity, Intensive insulin therapy, Liraglutide, Type 2 diabetes

Introduction

Type 2 diabetes is a progressive disease that creates a vicious cycle of glucotoxicity, and it is important to break the cycle and normalize glucose metabolism by initiating early treatment. Intensive insulin therapy with multiple insulin injections is considered effective for removing the glucotoxicity caused by hyperglycemia [1], and such removal has been performed in many patients with hyperglycemia under hospitalization and frequent self-monitoring of glucose. However, intensive insulin therapy can increase the risk of adverse reactions such as hypoglycemia and body weight gain.

Glucagon-like peptide-1 (GLP-1) receptor agonists are type 2 diabetes drugs that can be used in combination with insulin therapy and contribute to the improvement of not only fasting blood glucose levels, but also postprandial blood glucose levels. Therefore, combined use of a GLP-1 receptor agonist with insulin,which mainly improves fasting blood glucose levels may enable better glycemic control [2]. In fact, greater reductions in glycated hemoglobin(HbA1c) were seen in patients who added a GLP-1 receptor agonist to insulin therapy and in those who added insulin therapy to a GLP-1 receptor agonist, compared with those who did not add either of these therapies [3–5]. However, the clinical effects of such combination therapies with simultaneous initiation of both drugs as the initial treatment have not been fully investigated.

In the present study, we retrospectively investigated the efficacy and safety of combination therapy with a GLP-1 receptor agonist (liraglutide) and long-acting insulin (insulin glargine) adopted as the initial treatment in patients with type 2 diabetes under moderate or severe hyperglycemic conditions.

Methods

Among patients with type 2 diabetes attending our hospital for hyperglycemia, a retrospective observational study was conducted in 20 patients who started combination therapy with liraglutide and insulin glargine between April and September 2015 as the initial treatment (Lira + IGla group) and 10 patients who started intensive insulin therapy with multiple insulin injections between September 2012 and July 2013 and who were matched by age and sex (MII group).

The dose of liraglutide was started at 0.3 mg/day and increased up to 0.9 mg/day once daily. The initial dose of insulin was 0.1 U/kg in most cases and adjusted as needed thereafter. Patients were examined every other month, and checked for random blood glucose levels, HbA1c, body mass index (BMI), body weight, serum lipids, liver function markers, and adverse events for 3 months in each group. Patients with obvious acute metabolic events were excluded.

The study was approved by the institutional review board of the Kanto Rosai Hospital. All participants gave their written informed consent.

Testing for differences in patient characteristics between the groups was performed by a z-test for the qualitative factor (sex) and an unpaired t-test for quantitative factors.

The changes in individual parameters within each group at 3 months after treatment and changes in blood glucose levels and HbA1c in the Lira + IGla group over time were evaluated using a paired *t*-test.

***Corresponding Author:** Prof. Kumiko Hamano, Department of Diabetes and Endocrinology, Kanto Rosai Hospital, 1-1 Kizukisumiyoshi, Nakahara, Kawasaki, Kanagawa 211-8510, Japan, E-mail: k-hamano@kantoh.rofuku.go.jp

Citation: Kurasaki K, Kigawa I, Sohara E, Hamano K (2016) Effects of Combination Therapy with Liraglutide and Insulin Glargine as the Initial Treatment for Hyperglycemic Patients with Type 2 Diabetes: An Observational Study. Int J Diabetes Clin Diagn 3: 121. doi: https://doi.org/10.15344/2394-1499/2016/121

Results

There were no large differences in the patient characteristics between the Lira + IGla group and the MII group, including age (48.2 ± 13.7 years vs. 54.7 ± 12.6 years, p=0.22), sex (male/female, 17/3 vs. 6/4, *p*=0.13), body weight (79.1 ± 14.4 kg vs. 70.2 ± 17.5 kg, *p*=0.15), BMI (27.3 ± 4.7 kg/m^2 vs. 26.1 ± 5.0 kg/m^2, *p*= 0.52), plasma glucose (253.1 ± 145.3 mg/dL vs. 291.7 ± 228.8 mg/dL, *p*= 0.58), and HbA1c (10.8 ± 1.7% vs. 10.9 ± 1.6%, *p*= 0.87), except for duration of diabetes (2.6 ± 3.0 years vs. 6.9 ± 5.6 years, *p*< 0.05).

The blood glucose levels and HbA1c were significantly decreased after 1, 2, and 3 months compared with baseline (Figure 1). Table 1 shows the changes from baseline to 3 months for all parameters. HbA1c and low-density lipoprotein cholesterol (LDL-C) were significantly decreased in the Lira + IGla group and the MII group. Significant improvements in body weight, BMI, blood glucose level, and alanine aminotransferase (ALT) was observed in the Lira + IGla group only. No significant differences were observed in the two groups for other parameters. The mean insulin dose at 3 months after treatment initiation was 7.6 ± 3.1 U/kg in the Lira + IGla group and 17.0 ± 15.4 U/kg in the MII group, being clearly higher in the MII group.

With regard to adverse events in the Lira + IGla group, there was no hypoglycemia that required emergency transportation/urgent hospitalization. Some patients required dose reduction of liraglutide because of gastrointestinal symptoms, but there were no adverse events leading to discontinuation of treatment.

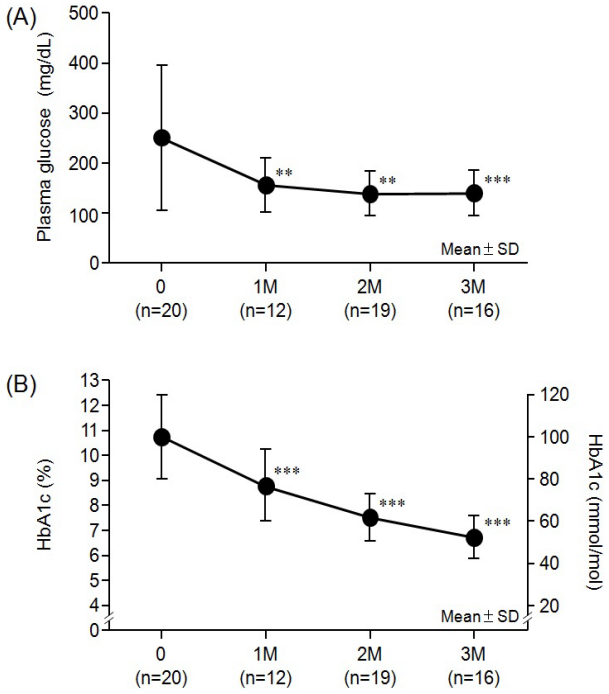

Figure 1: Mean changes in plasma glucose and HbA1c in the Lira + IGla group. (A) Plasma glucose. (B) HbA1c. **p<0.01, ***p<0.001,significant difference for mean change from baseline (paired t-test).

	Lira + IGla			MII		
	Mean ± SD (n)		Mean change from baseline (95% CI) *p*-value, (n)	Mean ± SD (n)		Mean change from baseline (95% CI) *p*-value (n)
	Baseline	3 months		Baseline	3 months	
Body weight (kg)	79.1 ± 14.4 (20)	73.6 ± 12.7 (15)	2.5 (0.6–4.4) <0.05 (15)	70.2 ± 17.5 (10)	73.9 ± 15.7 (8)	0.1 (−2.8–2.9) 0.95 (8)
BMI (kg/m^2)	27.3 ± 4.7 (20)	25.4 ± 3.6 (15)	0.9 (0.2–1.6) <0.05 (15)	26.1 ± 5.0 (10)	27.3 ± 5.2 (8)	0.0 (−1–1.1) 0.92 (8)
Plasma glucose (mg/dL)	253.1 ± 145.3 (20)	142.3 ± 45.5 (16)	74.5 (49.5–99.5) <0.001 (16)	291.7 ± 228.8 (10)	145.7 ± 49.6 (10)	146.0 (−27.6–319.6) 0.09(10)
HbA1c (%)[mmol/mol]	10.8 ± 1.7 [94.5 ± 18.6] (20)	6.8 ± 0.9 [50.8 ± 9.8] (16)	3.9 (3.1–4.8) [19.1(10.4–28.9)] <0.001 (16)	10.9 ± 1.6 [95.6 ± 17.5] (10)	6.7 ± 0.8 [49.7 ± 8.7] (10)	4.2 (2.7–5.7) [22.4(6.0–38.8)] <0.001 (10)
HDL-C (mg/dL)	46.8 ± 11.7 (18)	50.6 ± 9.8 (16)	1.6 (−4–7.1) 0.55 (14)	54.8 ± 26.8 (10)	56.7 ± 24.0 (10)	1.9 (−4.2–8) 0.50(10)
LDL-C (mg/dL)	144.7 ± 43.2 (18)	124.7 ± 32.6 (16)	27.2 (14.6–39.8) <0.001 (14)	127.6 ± 57.6 (10)	101.9 ± 41.4 (10)	25.7 (0.3–51.1) <0.05 (10)
TG (mg/dL)	295.0 ± 337.8 (18)	244.2 ± 263.6 (16)	40.5 (−12.6–93.6) 0.12 (14)	186.4 ± 101.9 (10)	157.2 ± 111.4 (10)	29.2 (−18.6–77.0) 0.20 (10)
AST (IU/L)	31.7 ± 21.3 (20)	21.1 ± 8.2 (16)	8 (−0.9–16.9) 0.08(16)	25.7 ± 24.7 (10)	24.6 ± 16.4 (10)	1.1 (−5.7–7.9) 0.72 (10)
ALT (IU/L)	43.9 ± 28.3 (20)	24.0 ± 8.7 (16)	16.8 (2.3–31.3) <0.05 (16)	28.6 ± 27.4 (10)	24.7 ± 15.7 (10)	3.9 (−8.8–16.6) 0.50 (10)

Table 1: Changes in variables in the two groups after 3 months

CI: confidence interval; HbA1c, glycated hemoglobin;BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Discussion

It has already been reported that better glucose-lowering effects can be obtained by additional administration of liraglutide in patients with type 2 diabetes on insulin therapy without developing hypoglycemia or weight gain, and that insulin requirements can be reduced [6–10]. It is very interesting that simultaneous and combined use of liraglutide and insulin glargine as the initial treatment in patients with type 2 diabetes under hyperglycemic or so-called glucotoxic conditions resulted in similar effects to those reported previously. The good glycemic control with a reduction in body weight obtained by combination therapy with liraglutide and insulin glargine may have had effects on lowering LDL-C or ALT.

Good glycemic control with low risks of hypoglycemia and body weight gain and low glucose excursions is required to prevent complications in patients with type 2 diabetes. The present observational study suggests that intensive insulin therapy is not necessarily required in patients with type 2 diabetes under moderate or severe hyperglycemic conditions and that liraglutide and insulin glargine combination therapy, which is superior in its glucose-lowering effects and is safe, simple, and less likely to cause weight gain, may be among the useful treatment options. Larger studies, such as prospective randomized controlled trials, are needed to further examine the usefulness of this combination therapy.

Competing Interests

The authors declare that they have no competing interests

Author Contributions

All authors contributed equally to this work. All authors contributed substantially to the study conception and design, as well as to the data acquisition and interpretation, and drafting of the manuscript.

References

1. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, et al (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res ClinPract 28:103-117.
2. Vora J (2013) Combining incretin-based therapies with insulin: realizing the potential in type 2 diabetes. Diabetes Care 36 Suppl 2: S226-232.
3. Balena R, Hensley IE, Miller S, Barnett AH (2013) Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. Diabetes Obes Metab 15: 485-502.
4. Holst JJ, Vilsbøll T (2013) Combining GLP-1 receptor agonists with insulin: therapeutic rationales and clinical findings. Diabetes Obes Metab 15: 3-14.
5. Eng C, Kramer CK, Zinman B, Retnakaran R (2014) Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 384: 2228-2234.
6. Lane W, Weinrib S, Rappaport J (2011) The effect of liraglutide added to U-500 insulin in patients with type 2 diabetes and high insulin requirements. Diabetes Technol Ther 13: 592-595.
7. Li CJ, Li J, Zhang QM, Lv L, Chen R, et al. (2012) Efficacy and safety comparison between liraglutide as add-on therapy to insulin and insulin dose-increase in Chinese subjects with poorly controlled type 2 diabetes and abdominal obesity. Cardiovasc Diabetol 11: 142.
8. Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de Loredo L, et al. (2015) Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. Diabetes ObesMetab 17: 1056-1064.
9. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahrén B, et al. (2015) Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ 351: h5364.
10. Seino Y, Kaneko S, Fukuda S, Osonoi T, Shiraiwa T, et al. (2016) Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36-week, randomized, double-blind, parallel-group trial. J Diabetes Investig 7: 565-573.