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New Era of Insulin Preparation for Once Weekly Administration

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Abstract

There was a new report for once-weekly Novo Nordisk's insulin icodec. After subcutaneous injection, the blood concentration reaches its maximum in 16 hours, and the half-life is about 1 week. The phase II clinical trial showed i) subjects were 247 type 2 diabetes, 59.6 ± 8.9 years, BMI 31.3 ± 4.6, HbA1c 8.0 ± 0.7%, FPG 181 ± 42 mg/dL, ii) For 26 weeks, HbA1c improved from 8.1% to 6.7% in group Ico and from 8.0% to 6.9% in group Gla with no significant difference, iii) significantly markers superior to Group Ico included changes in the mean daily glucose profile and time period of 70-140 mg/dL by CGM. Insulin icodec will hopefully develop smooth next phase trial.

Keywords: ***Insulin icodec; Phase II clinical trial; Treating to target in type 2 diabetes (4-T) trial; Insulin glargine; Food and drug administration (FDA)***

Diabetes has become a major medical, social and economic impact in any country across the world [1]. Among them, Continuous Glucose Monitoring (CGM) can be found as the development of diagnostic technology [2]. As a diet, attempts have been made from calorie restriction (CR) to low carbohydrate diet (LCD) [3]. Furthermore, DPP-4 inhibitors and SGLT2 inhibitors have been prevalent as oral hypoglycemic agents (OHAs) [4]. GLP-1 receptor agonists have appeared as injectable agent, and drugs that can be administered once a day to once a week have appeared [5]. With regard to insulin, insulin administered once a day has appeared as a long-acting type [6]. A combination of both of GLP-1 receptor agonist and insulin (Xultophy), which is administered once daily, has already been clinically applied [7,8].

Along with this transition of treatment, the algorithm of antidiabetic agents has changed significantly [9,10]. Furthermore, the reported effects of GLP-1 receptor agonists and SGLT2 inhibitors on cardiovascular outcomes have pointed out that they may be involved in the treatment of hypertension and heart disease in addition to diabetes [11,12]. Under these circumstances, insulin preparations are still in the position of the strongest medicine for controlling the blood glucose variability. Recently, there was a new report for a weekly dose of insulin [13]. Since this is a major topic and the agent will be possibly widely used for medical practice in the future, this article outlines the general development of insulin.

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There was formerly the Treating To Target in Type 2 Diabetes (4-T) Trial [14]. Since 4-T trial, it has been generalized to start diabetic treatment with a long-acting soluble insulin analog [15]. Its duration was approximately 40 hours at the most, and usual treatment method has been an injection once a day. At that time, the patients showed high satisfaction for only one injection. In recent years, weekly GLP-1 receptor agonists are more satisfying than once-daily injection [16]. Insulin treatment has been desired to be prepared once a week for long years. Among them, an insulin preparation once a week has been developed in a phase II clinical trial [13]. It was recently reported with satisfactory results, and then its outline will be described in this article.

The weekly insulin formulation currently under development is Novo Nordisk's insulin icodec. After subcutaneous injection, the blood concentration reaches its maximum in 16 hours, and the half-life is about 1 week. Subjects are type 2 diabetic (T2D) patients aged 18-75 years, taking metformin with HbA1c 7.0%-9.0%. Candidates for registration were divided into two groups, which are Icodec (Ico) and Glargine (Gla) groups [13]. Regarding the method, the Ico group started administration of insulin icodec once a week from 70 units/week. The Gla group started with 10 units/day of long-acting insulin glargine once daily, and the dose was adjusted so that fasting plasma glucose (FPG) was 70 mg/dL-108 mg/dL. The primary endpoint was the change in HbA1c at 26-week, and the secondary endpoints included FPG, body weight, mean blood glucose 9 tests/day, mean insulin administration and glucose availability by CGM during 24-26 weeks [13].

The subjects studied were totally 247, in which 139 males (56.3%), age 59.6 ± 8.9 years, morbidity 9.7 ± 7.4 years, BMI 31.3 ± 4.6, HbA1c 8.0 ± 0.7%, FPG 181 ± 42 mg/dL. During the 26-week period, the average HbA1c improved from 8.1% to 6.7% in group Ico and from 8.0% to 6.9% in group Gla. The difference in improvement between the two groups was -0.18% (95% CI -0.38 to + 0.02%, P=0.08), which was not statistically significant. In other words, group Ico shows the same or better blood glucose improving effect and safety than group Gla. As other endpoints at 26 weeks, the proportion of Ico and Gla groups with HbA1c less than 7% was 72% vs 68%, and less than 6.5% was 49% vs 39%, showing no significant difference. On the other hand, the markers significantly superior to Group Ico were changes in the mean value of daily glucose profile, mean insulin dose in the last 2 weeks, and the time period of 70 mg/dL -140 mg/dL of glucose by CGM [13].

In comparison with Ico vs Gla group, 1st degree hypoglycemia (54 mg/dL -69 mg/dL) was 368 in 125 cases vs 148 in 46 cases, showing significantly higher in Ico group. For 2nd to 3rd degree hypoglycemia, there was no significant difference between 38 in 20 cases vs 32 in 12 cases in two groups. Based on the above, Ico showed the efficacy as equivalent to Gla, and further evaluation of efficacy and safety in Phase III study will be needed.

There are historical changes in the treatment of diabetes. Previously, the introduction of insulin injections for T2D was generally mixed insulin 2 times a day [17]. After the report of the Kumamoto study, intensive insulin therapy (IIT) was recommended also for T2D as well as T1D [18]. However, questions were raised as to whether the difference in glycemic

control was apparent between them [19,20]. The results revealed that there was no difference in glycemic control and that the mixed injection two times was superior from the viewpoint of QOL [21,22].

Subsequently, 4-T study revealed that single injection of long-acting insulin was comparable to 2-3 injections daily treatment, with less frequent hypoglycemia [15]. There is also a suggestion of lower hypoglycemic risk in the ACCORD study [23], and then introduction of single injection of long-acting insulin has been common for the last 10 years.

As long-acting soluble insulin, there have been insulin glargine (U-100, U-300), insulin degludec and insulin detemir. Among them, former two would be rather prevalent because of ultra-long-acting mechanism. There is no doubt that fewer number of injections will contribute to better QOL or treatment satisfaction. If that provides equivalent glycemic control, then most basal insulin injections may be replaced by insulin icodec for actual diabetic practice in the future.

In summary, insulin icodec, a once-weekly injection-type insulin was introduced in this article. This is the first paper of insulin icodec, and further studies on safety will be required from now. Furthermore, the US Food and Drug Administration (FDA) recently announced a draft revision of its approval rules for antidiabetic agents [24]. It may change the policy that required cardiovascular outcomes investigation. Novo Nordisk that developed Icodec currently, had been asked to perform the DEVOTE test on insulin degludec before [25]. The company will hopefully make most advantage of previous experience and manage insulin icodec carefully and proceed smoothly in the future diabetic practice.

Conflicts of Interest

None

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REFERENCES

1. International Diabetes Federation. IDF DIABETES ATLAS Ninth edition. 2019. http://www.diabetesatlas.org/
2. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593-1603.
3. Bando H, Ebe K, Muneta T, et al. Effect of low carbohydrate diet on type 2 diabetic patients and usefulness of M-value. Diabetes Res Open J. 2017;3(1): 9-16.
4. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020;43(Suppl 1):S98-110.
5. Takehisa Y and Bando H. Elderly diabetic patients with effective add-on therapy of dulaglutide as a GLP-1 receptor analogue (GLP1 RA). Edel J Biomed Res Rev. 2020;2(1):31-5.
6. Taki K, Koyanagi M, Nagaoka S, et al. Treatment satisfaction, safety, and effectiveness of biosimilar insulin glargine is comparable in patients with type 2 diabetes mellitus after switching from insulin glargine or insulin degludec: a post-marketing safety study. Curr Med Res Opin. 2020;36(12):1975-83.
7. Heo YA. Insulin degludec/liraglutide in type 2 diabetes: a profile of its use. Drugs Ther Perspect. 2020;36:219-29.

8. Fujikawa T, Kato Y, Bando H, et al. The Administration of Xultophy for Diabetic Patients on Hemodialysis. Diab Res Open Access. 2020;2(3):72-8.
9. Nathan DM, Buse JB, Davidson MB, et al. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193-203.
10. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm: 2019 executive summary. Endocr Pract. 2019;25(1):69-100.
11. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
12. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-2701.
13. Rosenstock J, Bajaj HS, Janež A, et al. Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment. N Engl J Med. 2020;383(22):2107-16.
14. Jenkins N, Hallowell N, Farmer AJ, et al. Initiating Insulin as Part of the Treating To Target in Type 2 Diabetes (4-T) Trial: An interview study of patients' and health professionals' experiences. Diabetes Care. 2010;33(10):2178-80.
15. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009;361(18):1736-47.
16. Takase T, Nakamura A, Yamamoto C, et al. Improvement in treatment satisfaction after switching from liraglutide to dulaglutide in patients with type 2 diabetes: A randomized controlled trial. J Diabetes Investig. 2019;10(3):699-705.
17. Hirsch IB, Bergenstal RM, Parkin CG, et al. A Real-World Approach to Insulin Therapy in Primary Care Practice. Clin Diabetes. 2005;23(2):78-86.
18. Ohkubo Y, Kishikawa H, Araki E, et al. 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 Clin Pract. 1995;28(2):103-17.
19. Hirao K, Arai K, Yamauchi M, et al. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). Diabetes Res Clin Pract. 2008;79(1):171-6.
20. Miyashita Y, Nishimura R, Nemoto M, et al. Prospective randomized study for optimal insulin therapy in type 2 diabetic patients with secondary failure. Cardiovasc Diabetol. 2008;7:16.
21. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. Diabetes Obes Metab. 2009;11(1):45-52.
22. Masuda H, Sakamoto M, Irie J, et al. Comparison of twice-daily injections of biphasic insulin lispro and basal-bolus therapy: glycaemic control and quality-of-life of insulin-naïve type 2 diabetic patients. Diabetes Obes Metab. 2008;10(12):1261-5.

23. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.
24. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2020) Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control Guidance for Industry. Guidances (Drugs) | FDA. 2020/March. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.
25. Marso SP, McGuire DK, Zinman B, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med. 2017;377(8):723-32.