Case of subcutaneous insulin resistance syndrome treated with ultra-rapid insulin lispro

Takahiro Ishii1, Akihiro Katayama1*, Mihiro Sue1, Remi Kuribayashi1, Masafumi Tenta1, Yuichi Matsushita1, Masaya Takeda1, Izumi Iseda1, Satomi Tani2, Kazuyuki Hida1

INTRODUCTION
Subcutaneous insulin resistance (SIR) syndrome has been characterized as a condition wherein a patient develops severe resistance to subcutaneous insulin injections, but normal sensitivity to intravenous insulin1. Reports have shown that treating SIR syndrome with a mixed infusion of insulin lispro and heparin (Lis + Hepa) improves insulin absorption and provides good glycemic control2,3. However, attention should be paid to adverse effects, such as bleeding tendencies, due to continuous heparin administration, albeit in smaller doses than usual. We speculated that ultra-rapid insulin lispro (URLi; Lyumjev®; Eli Lilly Japan K.K., Kobe, Japan), which contains treprostinil and citrate, would provide good insulin absorption from the subcutis due to its similarity to heparin. We herein report our experience with URLi in a patient with SIR syndrome treated with Lis + Hepa.

CASE REPORT
A 40-year-old Japanese woman (92.0 kg; body mass index 36.5; glycated hemoglobin 8.9%) with type 2 diabetes mellitus was admitted to Okayama Medical Center, Okayama, Japan, for treatment modification. She was diagnosed with type 1 diabetes mellitus at the age of 16 years and was thereafter started on insulin injection therapy; however, due to recurrent diabetic ketoacidosis, continuous subcutaneous insulin infusion (CSII) was initiated. Unfortunately, her hyperglycemia persisted even after introducing CSII, which necessitated continuous venous insulin infusion for lowering blood glucose.

The patient was first admitted to our hospital at the age of 29 years due to hyperglycemia and severe insulin resistance (66.0 kg; body mass index 26.2), during which her glycated hemoglobin was 11.5%, despite high doses of insulin (210 U/day of insulin glargine, 50 U of regular insulin before each meal and 270 U/day of regular insulin with CSII; total daily dose [TDD] of 630 U/day). No obvious abnormal eating habits could be identified. Both glutamic acid decarboxylase and insulinoma antigen-2 antibodies were negative, and insulin antibody was 3.4% (reference value <0.4%). The glucagon stimulation test showed a change in C-peptide immunoreactivity (6 min) of 1.1 ng/mL (from 1.5 to 2.6 ng/mL).

Based on the aforementioned results, a diagnosis of type 2 diabetes with severe insulin resistance, and not type 1 diabetes, was established. As such, we subsequently changed the patient’s subcutaneous injections to continuous venous insulin infusion of regular insulin and markedly reduced her TDD from 630 to 100–120 U/day; furthermore, she was clinically diagnosed with SIR syndrome. Based on previous reports showing that Lis + Hepa was effective for SIR syndrome, we switched from...
continuous venous insulin infusion to CSII of Lis + Hepa\(^2,3\) (1:1 in volume, with final insulin lispro and heparin concentrations of 50 and 500 U/mL, respectively). Consequently, she was discharged with favorable glycemic control on CSII of Lis + Hepa (TDD 117 U/day).

Despite having continuously received a combination of Lis + Hepa for ~11 years, the patient suffered from suggillation and menorrhagia, which were thought to be caused by continuous heparin administration. As such, the patient requested to be hospitalized for modification of her treatment. On admission, she was treated with CSII of Lis + Hepa with a TDD of 55 U/day. Her laboratory findings and diabetic complication are shown in Table 1. We considered switching from Lis + Hepa to URLi, given that URLi contains treprostinil and citrate, and is more easily absorbed than insulin lispro alone. After fasting overnight, Lis + Hepa 0.2 U/kg or URLi 0.2 U/kg was subcutaneously administered followed by plasma glucose and serum insulin levels’ assessment.

Notably, the present results showed that although URLi promoted slightly higher serum insulin levels compared with in Lis + Hepa, both had a comparable glucose-lowering effect (Figure 1). These results showed that switching from Lis + Hepa to URLi would allow the patient to maintain at least similar levels of glycemic control while also maintaining quality of life. She was discharged on CSII of URLi (TDD 43 U/day), and showed marked improvement in glycemic control with thorough diet and exercise at home (Figure 2).

Following the change in treatment, suggillation and menorrhagia disappeared, although pain during injection was slightly increased.

**DISCUSSION**
Severe insulin resistance to subcutaneous insulin injection with normal intravenous insulin sensitivity, absence of elevated serum insulin levels after subcutaneous injection and increased insulin degradation in subcutaneous tissues characterizes SIR syndrome\(^4\). However, confirming insulin degradation enhancement remains challenging, with several cases requiring clinical diagnosis\(^5\). As previously reported\(^2,3\), treatment with a mixture of Lis + Hepa promoted good glycemic control for patients with SIR syndrome. Although the present case showed reasonably good blood glucose control by Lis + Hepa, she suffered from bleeding tendencies, which impaired her quality of life; therefore, after examining the glucose-lowering effect and absorption rate of URLi, we observed that it was comparable to those of Lis + Hepa and that switching to URLi was feasible.

Two mechanisms have been suggested to explain the effects of Lis + Hepa on SIR syndrome. First, insulin lispro is absorbed into the bloodstream more rapidly than regular insulin\(^6\). Second, heparin facilitates the diffusion of water-soluble molecules by bearing many negative charges\(^7\), and binds to vascular endothelial growth factors, which induce the permeabilization of the blood vessels\(^8,9\), thereby facilitating the transfer of subcutaneously injected insulin into the bloodstream. URLi is a

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**Table 1 | Laboratory findings and diabetic complications on admission**

| CBC         | Biochemistry          |
|-------------|-----------------------|
| WBC 7,000 /µL | TP 7.4 g/dL           |
| RBC 413 × 10\(^6\) /µL | Alb 4.3 g/dL         |
| Hb 11.5 g/dL | AST 29 IU/L           |
| Hct 36.7 %   | ALT 20 IU/L           |
| Plt 24.1 × 10\(^9\) /µL | γ-GTP 48 IU/L          |
| Coagulation  |                       |
| APTT 29.4 s | BUN 14 mg/dL          |
| PT 9.3 s    | Cre 0.78 mg/dL        |
| PT-INR 0.89 | PG 400 mg/dL          |
| Urine       |                        |
| Protein (+) | HbA1c 8.9 %           |
| Glucose (++)| Diabetic complications |
| Ketone (−)  | Peripheral neuropathy |
| ACR 607.0 mg/gCre | Autonomic neuropathy |
|             | Nephropathy Macroalbuminuria |

γ-GTP, γ-glutamyltransferase; ACR, albumin-to-creatinine ratio; Alb, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; Cre, creatinine; Hb, hemoglobin; HbA1c, glycated hemoglobin; Hct, hematocrit; PG, plasma glucose; Plt, platelet; PT, prothrombin time; PT-INR, international normalized ratio of prothrombin time; RBC, red blood cell; TP, total protein; WBC, white blood cell.
novel insulin formulation that adds two locally acting excipients, treprostinil and citrate, to insulin lispro. Treprostinil is a PGI2 analog that has a direct vasodilator effect and has been used as a therapeutic agent for pulmonary arterial hypertension, and citrate increases local vascular permeability. The addition of these two additives increases local blood flow and accelerates the transportation of injected insulin from the subcutaneous to the bloodstream, which might explain why URLi shows comparable insulin absorption effects as heparin.

In conclusion, we herein report a case of SIR syndrome that achieved good glycemic control with a novel insulin formulation. Although reports have shown that the combination of Lis + Hepa is effective for SIR syndrome, the present report shows that URLi might provide good glycemic control without the use of heparin.

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DISCLOSURE
The authors declare no conflict of interest.

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Figure 2 | Continuous glucose monitoring data and time in range (a) 3 weeks before admission and (b) 3 weeks after discharge.
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