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ORIGINAL ARTICLE

A multicenter, open-label, single-arm trial of the long-term safety of empagliflozin treatment for refractory diabetes mellitus with insulin resistance (EMPIRE-02)

Yushi Hirota[1], Yasumasa Kakei[2], Junta Imai[3], Hideki Katagiri[3], Ken Ebihara[4], Jun Wada[5], Junichi Suzuki[6], Tatsuhiko Urakami[6], Takashi Omori[7], Wataru Ogawa[1]*

[1]Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [2]Clinical and Translational Research Center, Kobe University Hospital, Kobe, Japan, [3]Department of Metabolism and Diabetes, Tohoku University Graduate School of Medicine, Miyagi, Japan, [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan, [5]Department of Nephrology, Rheumatology, Endocrinology, and Metabolism, Faculty of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama, Japan, [6]Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan, and [7]Division of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Keywords
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***Correspondence**
Wataru Ogawa
Tel.: +81-78-382-5860
Fax: +81-78-382-2080
E-mail address:
ogawa@med.kobe-u.ac.jp

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ABSTRACT

Aims/Introduction: Insulin resistance syndrome and lipoatrophic diabetes are rare conditions characterized by the development of treatment-refractory diabetes with severe insulin resistance. We recently conducted a 24 week, multicenter, single-arm trial (EMPIRE-01) that demonstrated a certain level of effectiveness and safety of empagliflozin for these conditions. To evaluate treatment safety over a longer period, we have now performed an additional 28 week trial (EMPIRE-02) that followed on from EMPIRE-01.

Materials and Methods: The primary and secondary outcomes were safety and efficacy evaluations, respectively. All eight subjects of the EMPIRE-01 trial participated in EMPIRE-02.

Results: Twenty adverse events (AEs) were recorded among five individuals during the combined 52 week treatment period of both trials. Whereas one case of chronic hepatitis B was moderate in severity, all other AEs were mild. There were thus no serious AEs or events necessitating discontinuation or suspension of treatment or a reduction in drug dose. Whereas ketoacidosis or marked increases in serum ketone body levels were not observed, the mean body mass of the subjects was decreased slightly after completion of EMPIRE-02. The improvement in mean values of glycemic parameters observed in EMPIRE-01 was not sustained in EMPIRE-02, mostly because of one individual whose parameters deteriorated markedly, likely as a result of nonadherence to diet therapy. The improvement in glycemic parameters was sustained during EMPIRE-02 after exclusion of this subject from analysis.

Conclusions: Empagliflozin demonstrated a certain level of safety and efficacy for the treatment of insulin resistance syndrome and lipoatrophic diabetes over 52 weeks, confirming its potential as a therapeutic option.

INTRODUCTION

Insulin resistance syndrome, formerly known as insulin receptor abnormalities[1,2], is traditionally classified into type A and type B, with type A being attributable to variants of the insulin receptor gene (*INSR*) and type B triggered by autoantibodies to the insulin receptor[3,4]. Given that variants of genes related to signaling downstream of the insulin receptor also give rise to conditions clinically similar to type A insulin resistance syndrome[5–7], the term "genetic insulin resistance syndrome"

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has recently been advocated to encompass disorders arising from variants either of the insulin receptor gene or of genes such as *PIK3R1* that are related to downstream signaling pathways[2]. Lipoatrophic diabetes is a genetic or acquired condition characterized by a marked systemic or localized reduction in the amount of adipose tissue[8,9]. This syndrome also manifests as several metabolic disorders including dyslipidemia, hepatic steatosis, and treatment-resistant diabetes, likely as a result of the loss of adipose tissue mass and derived humoral factors that regulate energy metabolism[10,11]. Given that both insulin resistance syndrome and lipoatrophic diabetes are rare conditions, information regarding the treatment of diabetes associated with them has been limited.

Empagliflozin exerts a glucose-lowering effect by inhibiting renal glucose reabsorption mediated by sodium–glucose cotransporter 2 (SGLT2)[12]. Given that the antidiabetic effects of such SGLT2 inhibitors are attributable to a mechanism independent of insulin action, these drugs might be expected to lower glycemia even in individuals with severe insulin resistance[6,13,14]. We recently performed a 24-week, multicenter, single-arm clinical trial (EMPIRE-01) to investigate the efficacy and safety of empagliflozin in eight individuals with insulin resistance syndrome or lipoatrophic diabetes[15]. This trial, which was conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, demonstrated that empagliflozin treatment was associated with a decrease in the hemoglobin A_{1c} (HbA_{1c}) level of 0.99 percentage points, from 8.46 ± 1.45% (mean ± SD) at baseline to 7.48 ± 1.26% at the end of the 24-week treatment period[15]. Seventeen adverse events (AEs) were noted in five subjects of the trial, with all of these AEs being mild and none necessitating discontinuation or suspension of treatment or a reduction in drug dosage[15].

The EMPIRE-01 trial, the first trial to investigate prospectively the clinical utility of an SGLT2 inhibitor for diabetes associated with insulin resistance syndrome or lipoatrophic diabetes in Japanese individuals, thus demonstrated a level of effectiveness and safety of empagliflozin for these rare conditions. To evaluate further the safety profile over a longer period, we conducted an additional 28 week trial (EMPIRE-02) following on from the 24 week EMPIRE-01 trial and investigated the frequency and severity of AEs over the combined 52 week study period.

MATERIALS AND METHODS

Study design

This nonrandomized, prospective, open-label, multicenter trial was conducted at five academic centers in Japan (Tohoku University Hospital, Nihon University Hospital, Jichi Medical University Hospital, Kobe University Hospital, and Okayama University Hospital). The trial adhered to the 2013 Declaration of Helsinki[16] and ICH-GCP guidelines[17]. Both the study protocol and the amendments received approval from the institutional review board at each site. The trial was registered with the Japan Registry of Clinical Trials (jRCTs 2051190094) and ClinicalTrials.gov (NCT 04221152). All participants provided written informed consent before entering the study.

Individuals diagnosed with insulin resistance syndrome or lipoatrophic diabetes who were aged 20 years or older and had an HbA_{1c} level of at least 7% (52 mmol/mol) were recruited for the study. Detailed inclusion and exclusion criteria as well as the diagnostic criteria for insulin resistance syndrome and lipoatrophic diabetes were described previously[15] and are also provided in Appendix S1. Study participants were treated with empagliflozin at a starting dose of 10 mg once daily per os. After 12 weeks of treatment, the dose was increased to 25 mg if the HbA_{1c} level remained at or above 7.0% (52 mmol/mol). The participants were requested not to alter the regimens for dietary and exercise therapy from those prior to the start of the trial. The effectiveness and safety of the treatment up to 24 weeks were described previously as the EMPIRE-01 trial[15]. The additional 28 week EMPIRE-02 trial was performed after completion of EMPIRE-01 (Figure S1). In the EMPIRE-02 trial, the administration of empagliflozin was continued at the same dosage level as that administered at the end of EMPIRE-01. Participants were followed up for monitoring of AEs and treatment efficacy at 12 and 28 weeks after initiation of the EMPIRE-02 trial, corresponding to 36 and 52 weeks, respectively, after initiation of EMPIRE-01.

Outcomes

The primary outcome of the EMPIRE-02 trial was the safety assessment including evaluation of AEs, adverse drug reactions (ADRs), rescue medication, and other key safety considerations. The latter considerations included hypoglycemia, urinary tract infection, genital infection, dehydration (including weight loss), polyuria or frequent urination, renal impairment, increased ketone body levels, cardiovascular risk, malignant tumor risk, and AEs of special interest, such as liver dysfunction, renal dysfunction, metabolic acidosis, ketoacidosis, diabetic ketoacidosis (DKA), and lower limb amputation.

Secondary outcomes focused on efficacy and included the percentage and absolute changes in HbA_{1c} level from baseline (before initiation of the EMPIRE-01 trial) to the end of the 28 week EMPIRE-02 trial period. HbA_{1c} and fasting plasma glucose (FPG) levels, as well as insulin dosage, were monitored at 12 and 28 weeks after initiation of the EMPIRE-02 trial (36 and 52 weeks after the initiation of EMPIRE-01). Changes in postprandial blood glucose levels were also assessed by continuous glucose monitoring (CGM).

Sample size

All eight participants who completed the EMPIRE-01 trial were recruited for EMPIRE-02.

Data analysis

We investigated the frequency and severity of AEs over the combined 52 weeks of the EMPIRE-01 and EMPIRE-02 trials.

The absolute and percentage changes in HbA_{1c} level as well as the change in FPG concentration at 52 weeks (at the end of the 28 week EMPIRE-02 trial) relative to baseline were assessed on an individual participant basis as well as summarized with sample size, mean, standard deviation (SD), minimum, median, and maximum values. The population means with 95% confidence intervals (CIs) of these changes were estimated. All statistical analysis was performed with the use of SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Participants

Seven individuals with genetic insulin resistance syndrome – four with variants of *INSR* and three with variants of *PIK3R1* – and one individual with lipoatrophic diabetes, who harbored a pathological variant of the *BSCL2* gene, participated in the EMPIRE-01 trial, as described previously[15] and are also provided in Table S1. Individuals with type B insulin resistance syndrome were not included in the trial. All of these individuals also participated in the EMPIRE-02 trial and completed the 28 week treatment course. During the EMPIRE-02 trial, two individuals were treated with 10 mg of empagliflozin per day and six received 25 mg of the drug in accordance with the dosing protocol.

Safety evaluation

A total of 20 AEs was noted in five individuals over the combined duration of 52 weeks of the EMPIRE-01 and EMPIRE-02 trials (Table 1). Whereas a case of chronic hepatitis B was moderate in severity, all other AEs were mild, with no serious AEs or events necessitating the discontinuation or suspension of treatment or a reduction in drug dose being reported. All 20 AEs had resolved or improved by the end of the trial. One case of mild hypoglycemia was reported as an ADR and was ameliorated by a reduction in the insulin dose administered. Whereas this event manifested with characteristic symptoms of hypoglycemia, the recorded blood glucose level at this time of onset was 91 mg/dL. Therefore, this event of hypoglycemia is categorized as Grade 1 (mild) according to the Ademolus Classification of Hypoglycemia[18]. This case of hypoglycemia was the only event reported as a key safety consideration. As an AE of special interest, liver dysfunction (aspartate [AST] or alanine [ALT] aminotransferase level of more than five times the upper limit of normal) was identified in two individuals; however, a causal relation between these events and the investigational drug was denied.

Figure 1 shows the time courses of the mean serum level of ketone bodies and mean body mass over the course of the study treatment. The body mass at the end of the EMPIRE-02 trial, which corresponds to 52 weeks after the initiation of the EMPIRE-01 trial, had declined by 1.68 ± 0.12 kg (mean ± SD) from baseline (before initiation of EMPIRE-01). The temporal changes in these parameters for each participant are shown in Figure S2. The serum level of ketone bodies exhibited an elevation in all eight participants at 24 weeks compared with the initiation of EMPIRE-01. By 52 weeks, these levels had increased in four individuals from their week 24 assessments, while the others exhibited a decrease. The body mass decreased in seven participants at 24 weeks compared with the initiation of EMPIRE-01. However, by 52 weeks, the body mass had increased in four of these individuals from their week 24 assessments, while the remaining participants manifested a decrease.

Table 1 | Adverse events associated with the study treatment

Event	Number	Case no.	Severity	Drug related	Study treatment
Nasopharyngitis	3	2, 2, 2	Mild	No	Continued
AST of >5× ULN	1	2	Mild	No	Continued
ALT of >5× ULN	2	2, 2	Mild	No	Continued
Contact dermatitis	1	2	Mild	No	Continued
Cough	1	4	Mild	No	Continued
Hypoglycemia	1	6	Mild	Yes	Continued
Hyperglycemia	1	6	Mild	No	Continued
Tenosynovitis	2	7, 8	Mild	No	Continued
Infectious enteritis	1	7	Mild	No	Continued
Diarrhea	2	7, 8	Mild	No	Continued
Nausea	1	8	Mild	No	Continued
Headache	1	8	Mild	No	Continued
Periarthritis	1	8	Mild	No	Continued
Chronic hepatitis B	1	7	Moderate	No	Continued
Parotitis	1	2	Mild	No	Continued

ULN, upper limit of normal.

Efficacy evaluation

The mean HbA_{1c} level for all study participants at 52 weeks after initiation of the EMPIRE-01 trial (mean ± SD: 7.91 ± 1.15% [62.6 ± 12.7 mmol/mol]) was 0.55 percentage points (5.8 mmol/mol) lower (95% CI of −0.41 to 1.51 percentage points or −4.4 to 15.9 mmol/mol) than that at baseline (8.46 ± 1.45% [68.4 ± 15.9 mmol/mol]). The percentage change in HbA_{1c} level from baseline to 52 weeks after treatment onset was −5.34% (95% CI, −17.31 to 6.63%). The time courses of the HbA_{1c} level for the study population (mean) and for each participant separately are shown in Figure 2a and Figure S3a, respectively. The HbA1c levels decreased in all eight participants at 24 weeks compared with the initiation of EMPIRE-01. Nevertheless, at 52 weeks, half of the individuals increased from their week 24 assessments, while the other half either maintained or showed further reductions.

The mean FPG concentration for all participants after treatment for 52 weeks (138.6 ± 40.0 mg/dL [7.70 ± 2.22 mmol/L])

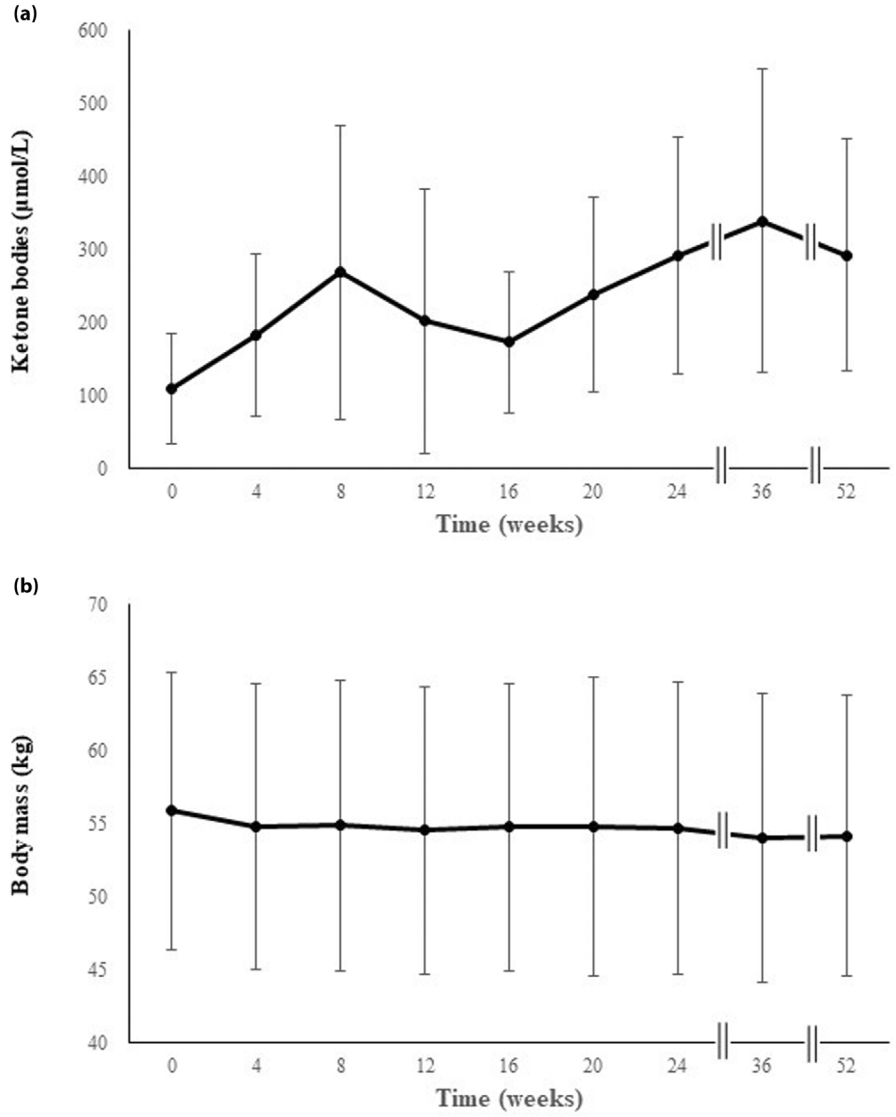

Figure 1 | Temporal changes in the mean serum level of ketone bodies (a) and mean body mass (b) during empagliflozin treatment for the study population. Data are mean ± SD (n = 8).

was 58.0 mg/dL (3.22 mmol/L) lower (95% CI of 19.0–97.0 mg/dL or 1.06–5.39 mmol/L) than that at baseline (196.6 ± 66.2 mg/dL [10.92 ± 3.68 mmol/L]). The time courses of FPG concentration for the study population as a whole and for each participant are shown in Figure 2b and Figure S3b, respectively. The FPG concentrations decreased in seven of the eight participants at 24 weeks compared with the initiation of EMPIRE-01. By the 52 week evaluation, six individuals showed an increase from their week 24 assessments, whereas two individuals noted a decrease.

As a result of the absence of the final CGM data for one individual (case 5), the CGM analysis was limited to seven individuals. The average sensor glucose level and time in range at 36 weeks were 169.1 ± 48.8 mg/dL (9.39 ± 2.71 mmol/L) and 57.0 ± 25.1%, respectively, whereas those at baseline were 175.1 ± 75.3 mg/dL (9.73 ± 4.18 mmol/L) and 56.3 ± 38.2%, respectively (Table 2).

Whereas the reduction in HbA_{1c} level was 0.99 percentage points (95% CI, 0.59–1.38 percentage points) or 10.8 mmol/mol (95% CI, 6.6–14.9 mmol/mol) at the end of the EMPIRE-01 trial[15], that at the end of EMPIRE-02 was 0.55 percentage points (95% CI, −0.41 to 1.51 percentage points). Analysis of the time-dependent change in HbA_{1c} level for each individual revealed that one individual (case 8, with genetic insulin resistance syndrome) experienced a rapid increase in this parameter after the end of the EMPIRE-01 trial (Figure S3a). The case

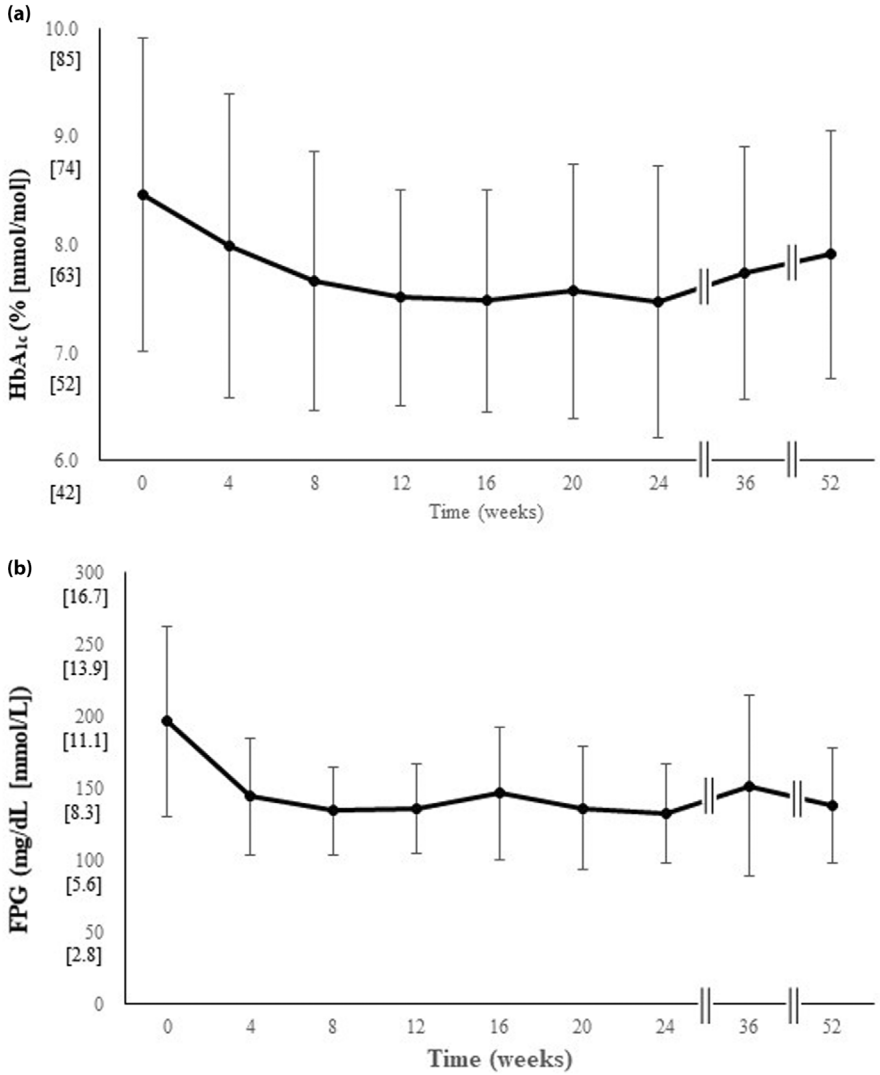

Figure 2 | Temporal changes in the mean HbA_{1c} level (a) and the mean FPG concentration (b) during empagliflozin treatment for the study population. Data are mean ± SD (n = 8).

Table 2 | CGM metrics at baseline as well as 20 and 36 weeks after treatment onset

Parameter	Day 0	Day 140	Day 252
Mean sensor glucose (mg/dL)	175.1 ± 75.3	145.0 ± 45.1	169.1 ± 48.8
Mean sensor glucose (mmol/L)	9.73 ± 4.18	8.06 ± 2.51	9.39 ± 2.71
CV of sensor glucose (%)	30.0 ± 4.7	29.8 ± 8.1	28.1 ± 4.5
Time above range (%)	40.3 ± 41.0	23.4 ± 24.0	39.3 ± 29.5
Time in range (%)	56.3 ± 38.2	70.4 ± 19.7	57.0 ± 25.1
Time below range (%)	3.4 ± 4.0	6.2 ± 9.3	3.7 ± 9.5

Data are mean ± SD (n = 7). CV, coefficient of variation.

report form showed that this individual began consuming one piece of pastry or sweet bread almost daily after the initiation of the EMPIRE-02 trial. As the trial protocol requested participants not to alter their dietary therapy conducted prior to the trial, we deemed this case as non-adherence to the dietary therapy. We therefore also analyzed the efficacy data for the seven cases remaining after exclusion of case 8.

The mean reduction in HbA_{1c} level for these seven individuals was 1.09 percentage points (95% CI, 0.70–1.47 percentage points) or 11.9 mmol/mol (95% CI, 8.0–15.7 mmol/mol) at the end of EMPIRE-01 and 0.90 percentage points (95% CI, 0.32–1.48 percentage points) or 9.6 mmol/mol (95% CI, 4.1–15.0 mmol/mol) at the end of EMPIRE-02 (Table S2). The

mean reduction in FPG concentration of the seven cases was 62.3 mg/dL (95% CI, 16.7–107.9 mg/dL) or 3.46 mmol/L (95% CI, 0.93–5.99 mmol/L) at the end of EMPIRE-01 and 58.4 mg/dL (95% CI, 11.86–105.0 mg/dL) or 3.25 mmol/L (95% CI, 0.66–5.83 mmol/L) at the end of EMPIRE-02 (Table S1).

Two participants were treated with multiple daily insulin injections. In one of these individuals, the total daily insulin dose and the total daily basal insulin dose had decreased from 89 to 52 U and from 40 to 24 U, respectively, during the initial treatment period of 24 weeks and remained at these lower values over the subsequent 28 weeks. In the second individual, although the total daily insulin dose had declined from 144 to 126 U after treatment for 52 weeks, the total daily basal insulin dose increased from 30 to 32 U over this period.

DISCUSSION

The 28 week EMPIRE-02 trial was undertaken primarily to investigate the long-term safety of empagliflozin and followed on from the 24 week EMPIRE-01 trial, which was the first study to assess the efficacy and safety of empagliflozin treatment for insulin resistance syndrome and lipoatrophic diabetes in accordance with ICH-GCP guidelines[15]. During the combined 52 week trial period, the 20 observed AEs were all mild, with the exception of a case of chronic hepatitis B. A causal relation between this latter moderate event and the investigational drug was denied, however. Our results therefore further confirm the safety of empagliflozin for the treatment of diabetes associated with insulin resistance syndrome or lipoatrophic diabetes. Whereas polyuria, volume depletion, genital infections, and urinary tract infections are often referred to as "characteristics AEs of SGLT2 inhibitors", recent pooled analyses of subjects treated with this class of drugs revealed that the frequency of polyuria, volume depletion, genital infections, and urinary tract infections are 1.29, 0.5–3.3, 0.1–2.4, and 0.6–6.9%, respectively[19–21]. Given the small cohort of only eight participants, the absence of these AEs aligns with anticipated statistical probabilities.

Neither DKA nor a substantial increase in the serum level of ketone bodies was observed during the EMPIRE-01 or EMPIRE-02 trials. Whereas the treatment of diabetes with SGLT2 inhibitors appears to be associated with an increased risk of DKA, its frequency is not high in treated individuals with type 1 or type 2 diabetes[22,23]. Insufficient action of insulin, due either to impaired insulin secretion or to insulin resistance, is related to the pathogenesis of DKA[24,25]. Caution is therefore warranted regarding the development of DKA during treatment of individuals with severe insulin resistance, such as those investigated in this study, with SGLT2 inhibitors.

Whereas insulin resistance is generally associated with obesity, both genetic insulin resistance syndrome and lipoatrophic diabetes are characterized by leanness. We detected a small reduction in mean body mass at the end of the EMPIRE-01 (−1.16 kg) and EMPIRE-02 (−1.68 kg relative to baseline) trials. This decrease in body mass is similar in extent to those reported in clinical trials of SGLT2 inhibitors for type 1 or type 2 diabetes[26–30]. However, given the leanness of individuals with these rare conditions, even such a small body mass reduction may warrant caution in the clinical setting.

With regard to efficacy evaluation, the mean reductions in glycemic parameters at the end of the 52 week treatment period were smaller than those apparent at the end of the 24 week treatment period. However, this difference was largely due to a marked deterioration in the glycemic parameters of one individual with genetic insulin resistance syndrome who ceased to adhere to dietary therapy; this individual began consuming one piece of pastry or sweet bread almost daily after the initiation of the EMPIRE-02 trial. Analysis of the data from the remaining seven participants revealed that the reductions in HbA_{1c} and FPG levels at 52 weeks were similar to those at 24 weeks. Evidence suggests that treating individuals with type 2 diabetes with SGLT2 inhibitors affects appetite or eating behavior[31,32]. We therefore cannot exclude the possibility that SGLT2 inhibitors also affect appetite in individuals with insulin resistance syndrome, potentially leading to nonadherence to dietary therapy during the course of treatment.

The small number of participants and its single-arm design are limitations of the present study. In Japan, the number of cases of genetic insulin resistance syndrome and lipoatrophic diabetes undergoing treatment at specialized institutions was recently estimated to be approximately 100 for each[5,33]. The rarity of these conditions therefore precludes the performance of trials with large numbers of participants. Insulin-like growth factor-1 and metreleptin are the only medications officially approved for the treatment of insulin resistance syndrome and lipoatrophic diabetes, respectively. The trials that served as the basis for the approval of these agents were also conducted with a relatively small number of subjects (eight and seven for insulin resistance syndrome and lipoatrophic diabetes, respectively)[34,35]. In addition, in many of our analyses, we combined the results from all eight subjects, which included seven individuals with insulin resistance syndrome and one with lipoatrophic diabetes. Given the distinct pathologies of these two conditions, combining them for analysis is not ideal.

In conclusion, the EMPIRE-01 and EMPIRE-02 trials have demonstrated a certain level of effectiveness and safety of empagliflozin for the treatment of diabetes associated with insulin resistance syndrome or lipoatrophic diabetes. Whereas the number of study participants was limited, the performance of the trials in accordance with ICH-GCP guidelines ensured their quality. Various rare conditions are accompanied by diabetes, making it challenging to identify appropriate treatments for all such conditions. The paucity of medical information about such conditions can also confer a serious psychological burden on affected individuals[36]. The results of the present study should prove helpful not only for healthcare providers caring for individuals with insulin resistance syndrome or lipoatrophic diabetes but also for alleviating the psychological issues faced by the affected individuals.

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DISCLOSURE

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Approval of the research protocol: The trial was performed in accordance with the 2013 Declaration of Helsinki and ICH-GCP guidelines. The study protocol and amendments were approved by Kobe University Hospital Institutional Review Board (No. 190020, approval date: October 23, 2019) and the relevant institutional review board at each additional study site (Tohoku University Hospital Institutional Review Board, The Institutional Review Board of Nihon University Hospital, Jichi Medical University Hospital Institutional Review Board, and IRB of Okayama University Hospital).

Informed consent: Informed consent was provided by each participant before entry into the study.

Registry and the registration no. of the study/trial: The trial was registered with the Japan Registry of Clinical Trials (jRCTs 2051190094) on January 15, 2020, and with ClinicalTrials.gov (NCT 04221152) on January 9, 2020.

Animal studies: N/A.

REFERENCES

1. Semple RK, Savage DB, Cochran EK, *et al*. Genetic syndromes of severe insulin resistance. *Endocr Rev* 2011; 32: 498–514.
2. Ogawa W, Araki E, Ishigaki Y, *et al*. New classification and diagnostic criteria for insulin resistance syndrome. *Diabetol Int* 2022; 13: 337–343.
3. Kahn CR, Flier JS, Bar RS, *et al*. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N Engl J Med* 1976; 294: 739–745.
4. Musso C, Cochran E, Moran SA, *et al*. Clinical course of genetic diseases of the insulin receptor (type a and Rabson-Mendenhall syndromes): a 30-year prospective. *Medicine (Baltimore)* 2004; 83: 209–222.
5. Takeuchi T, Ishigaki Y, Hirota Y, *et al*. Clinical characteristics of insulin resistance syndromes: a nationwide survey in Japan. *J Diabetes Investig* 2020; 11: 603–616.
6. Hamaguchi T, Hirota Y, Takeuchi T, *et al*. Treatment of a case of severe insulin resistance as a result of a PIK3R1 mutation with a sodium-glucose cotransporter 2 inhibitor. *J Diabetes Investig* 2018; 9: 1224–1227.
7. Kushi R, Hirota Y, Ogawa W. Insulin resistance and exaggerated insulin sensitivity triggered by single-gene mutations in the insulin signaling pathway. *Diabetol Int* 2020; 12: 62–67.
8. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004; 350: 1220–1234.
9. Brown RJ, Araujo-Vilar D, Cheung PT, *et al*. The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *J Clin Endocrinol Metab* 2016; 101: 4500–4511.
10. Garg A. Clinical review: lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab* 2011; 96: 3313–3325.

11. Chiquette E, Oral EA, Garg A, *et al*. Estimating the prevalence of generalized and partial lipodystrophy: findings and challenges. *Diabetes Metab Syndr Obes* 2017; 10: 375–383.
12. Grempler R, Thomas L, Eckhardt M, *et al*. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab* 2012; 14: 83–90.
13. Kawana Y, Imai J, Sawada S, *et al*. Sodium-glucose cotransporter 2 inhibitor improves complications of lipodystrophy: a case report. *Ann Intern Med* 2017; 166: 450–451.
14. Nagashima S, Wakabayashi T, Saito N, *et al*. Long-term efficacy of the sodium-glucose cotransporter 2 inhibitor, ipragliflozin, in a case of type a insulin resistance syndrome. *J Diabetes Investig* 2020; 11: 1363–1365.
15. Hirota Y, Kakei Y, Imai J, *et al*. A multicenter, open-label, single-arm trial of the efficacy and safety of empagliflozin treatment for refractory diabetes mellitus with insulin resistance (EMPIRE-01). *Diabetes Ther* 2024; 15: 533–545.
16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research. *JAMA* 2013; 310: 2191–2194.
17. European Medicines Agency, International Conference on Harmonisation. Guideline for good clinical practice E6 (R2) —step 5. 1 December 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf Accessed May 29, 2019.
18. Ademolu AB. Analysis of hypoglycemic episodes in diabetics in Africans using Ademolus Classification of Hypoglycemia (ACH). *Acta Sci Med Sci* 2019; 3: 138–145.
19. Kinduryte Schorling O, Clark D, Zwiener I, *et al*. Pooled safety and tolerability analysis of empagliflozin in patients with type 2 diabetes mellitus. *Adv Ther* 2020; 37: 3463–3484.
20. Yabe D, Yasui A, Ji L, *et al*. Safety and tolerability of empagliflozin in east Asian patients with type 2 diabetes: pooled analysis of phase I–III clinical trials. *J Diabetes Investig* 2019; 10: 418–428.
21. Kaku K, Yamamoto K, Fukushima Y, *et al*. Safety and effectiveness of empagliflozin in Japanese patients with type 2 diabetes: final results of a 3-year post-marketing surveillance study. *Expert Opin Drug Saf* 2022; 21: 1315–1328.
22. Bonora BM, Avogaro A, Fadini G. Sodium-glucose cotransporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature. *Diabetes Obes Metab* 2018; 20: 25–33.
23. Peters AL, Henry RR, Thakkar P, *et al*. Diabetic ketoacidosis with canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. *Diabetes Care* 2016; 39: 532–538.
24. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Investig* 2016; 7: 135–138.
25. Ogawa W, Hirota Y. Sodium-glucose cotransporter 2 inhibitor-associated diabetic ketoacidosis in patients with type 1 diabetes: metabolic imbalance as an underlying mechanism. *J Diabetes Investig* 2019; 10: 879–882.
26. Roden M, Weng J, Eilbracht J, *et al*. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2013; 1: 208–219.
27. Ridderstråle M, Andersen KR, Zeller C, *et al*. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2014; 2: 691–700.
28. Kovacs CS, Seshiah V, Swallow R, *et al*. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2014; 16: 147–158.
29. Mathieu C, Dandona P, Gillard P, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care* 2018; 41: 1938–1946.
30. Araki E, Watada H, Uchigata Y, *et al*. Efficacy and safety of dapagliflozin in Japanese patients with inadequately controlled type 1 diabetes (DEPICT-5): 52-week results from a randomized, open-label, phase III clinical trial. *Diabetes Obes Metab* 2020; 22: 540–548.
31. Masuda T, Watanabe Y, Fukuda K, *et al*. Unmasking a sustained negative effect of SGLT2 inhibition on body fluid volume in the rat. *Am J Physiol Renal Physiol* 2018; 315: F653–F664.
32. Miura H, Sakaguchi K, Okada Y, *et al*. Effects of ipragliflozin on glycemic control, appetite and its related hormones: a prospective, multicenter, open-label study (SOAR-KOBE study). *J Diabetes Investig* 2019; 10: 1254–1261.
33. Tanaka T, Kusakabe T, Ebihara K, *et al*. Practice guideline for lipodystrophy syndromes–clinically important diseases of the Japan Endocrine Society (JES). *Endocr J* 2021; 68: 1027–1042.
34. Kuzuya H, Matsuura N, Sakamoto M, *et al*. Trial of insulinlike growth factor I therapy for patients with extreme insulin resistance syndromes. *Diabetes* 1993; 42: 696–705.
35. Ebihara K, Kusakabe T, Hirata M, *et al*. Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007; 92: 532–541.
36. Yagi N, Toda A, Mitani K, *et al*. A qualitative research study of experiences and perceptions of people living with insulin resistance syndrome or lipoatrophic diabetes in Japan. *Diabetes Ther* 2023; 14: 1345–1356.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. | Methods.

Figure S1. | Study design and visit plan.

Figure S2. | Time courses of the serum concentration of ketone bodies (a) and body mass (b) for individual participants during empagliflozin treatment.

Figure S3. | Time courses of HbA_{1c} (a) and FPG (b) levels for individual participants during empagliflozin treatment.

Table S1. | Clinical information for the study participants with insulin resistance syndrome or lipoatrophic diabetes

Table S2. | Mean HbA_{1c} and FPG concentrations for the study subjects after exclusion of case 8