Comparison of the safety and clinical efficacy of glucagon-like peptide-1 receptor agonist and α-glucosidase inhibitor among Chinese people with type 2 diabetes

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Abstract

Purpose: To compare the safety and efficacy of once-weekly prescription of GLP-1 receptor agonists (adlyxin) with those of α-glucosidase inhibitor (voglibose) and other reference drugs (RD).

Methods: A total of 1250 stable diabetes-mellitus patients from the Department of Endocrinology, Ningbo No. 6 Hospital, Ningbo, Zhejiang 315040, China were enrolled in this study between Feb 2018 and Jan 2020. They were treated using physical exercise and diet chart therapy. The patients were assigned to three different groups and administered GLP-1 receptor agonist (GLP-1RA) or glucosidase inhibitor (voglibose) and other reference drugs (RDs). The safety and efficacy of these drugs were compared. The primary endpoint was the number of treatment-emergent adverse events (TEAEs), while the secondary endpoints were based on symptomatic hypoglycaemic episodes and other biochemical parameters.

Results: Patients who used α-glucosidase inhibitors had the highest percentage of TEAEs, when compared to those on GLP-1RAs and RDs (p < 0.05). No specific cases of severe hypoglycaemia were observed among all the groups. Users of adlyxin also achieved significant glycaemic control at the end of the study period, when compared to voglibose users, with a mean HbA1c baseline of 8.2 % (p < 0.05).

Conclusion: These results indicate that the GLP-1 receptor agonist adlyxin achieved good glycaemic control. Thus, it has beneficial potential for use among type 2 diabetes in the Chinese population.

Keywords: Adlyxin, GLP-1 receptor agonist, Type 2 diabetes, Glycaemic control, α-Glucosidase inhibitors

INTRODUCTION

The sharp increase in the number of type 2 diabetes (T2D) patients globally may be due to obesity and physical inactivity [1]. There is also an increase in the number of T2D patients among the Asian population, mostly in China [2]. In the Chinese population, the sudden increase in T2D population may be because of better economic development, population growth, aging, and Westernized lifestyle [3].
Diabetes mellitus or T2D is a progressive metabolic disease which is characterized by hyperglycemia and insulin deficiency [4]. The complications caused by T2D have become such a global health issue that there is urgent need for the prevention and management of the disease [5]. In spite of various antidiabetic drug classes that have been approved for T2D patients, the ultimate therapeutic goals for T2D are yet to be fully achieved. Thus, there is need for the development of a novel therapeutic approach that will be more efficient than the existing ones. Several drug classes for good glycaemic control and effective long-term use are already available in the market. However, the problem of excess mortality and morbidity still remain serious medical concerns [6,7]. When the onset of T2D is mostly influenced by obesity and lack of physical activity, glycaemic control drugs are generally recommended.

The commonly used therapies for glycaemic control are glucagon-like peptide 1 (GLP-1) agonists, α-glucosidase inhibitor, dipeptidyl peptidase 4 (DPP-4), and sodium/glucose cotransporter 2 (SGLT-2) inhibitors [8]. However, the various classes of drugs are ineffective in achieving the recommended glycaemic level, which is still a challenge for many patients. Hence, it is very important to customize each treatment based on control of weight gain and achievement of glycaemic targets. In fact, glucagon-like peptide-1 receptor agonists (GLP1RAs) are known for achieving glycaemic control by reducing body weight, relative to other T2D therapies [9]. Moreover, there are several studies on comparative clinical and cost-effective analysis on DPP4 and SGLT inhibitors. However, not much is known on comparative clinical efficacy of glucagon-like peptide 1 (GLP-1) agonists and α-glucosidase inhibitors, and their optimal treatments [10-12]. Therefore, the present study was aimed at comparing the safety and efficacy of once-weekly prescription of GLP-1 receptor agonists (adlyxin) with those of α-glucosidase inhibitor (voglibose) monotherapy (1.0 mg) and other reference drugs.

**EXPERIMENTAL**

**Ethical statement and approval**

All procedures were carried out in accordance with the Declaration of Helsinki 1964 and its later amendments [13]. Written informed consent was provided by all patients and participants. Consent was obtained from each subject regarding their personal information on demographic factors, and any other history of medical condition using a questionnaire. All protocols and procedures were approved by the institutional Medical Ethical Research Committee (approval no. NH/End/34613-43C).

**Study population**

A total of 1250 stable diabetes mellitus patients at the Ningbo No.6 Hospital, Ningbo, Zhejiang, China, 315040 between February 2018 and January 2020 who were treated with physical exercise, diet chart therapy and prescription of GLP-1 receptor agonists (adlyxin) or glucosidase inhibitor (voglibose) and other reference drugs, were investigated. The study population comprised patients in the age group of 40 - 70 years, with HbA1c levels between 50 and 90 mmol/mol during the screening period. Patients who developed chronic diseases such as renal impairment, vascular diabetes and pancreatitis were excluded from the study.

**Grouping and treatment**

The participants were assigned to three different groups treated with GLP-1 receptor agonists or α-glucosidase inhibitor or RD. Initially, all the groups were subjected to a mandatory 10-week diet and exercise therapy. Group 1 received 1.0 mg of α-glucosidase inhibitor (voglibose), while group 2 was given 1.0 mg of GLP-1 receptor agonist (adlyxin). The third group received 1.0 mg of RD such as insulin or acarbose, once a week for 24 months. Follow-up continued till the end of the study. The drugs were administered once weekly via subcutaneous injection in the thigh, abdomen, or upper arm, on the same day of the week.

**Endpoint/outcome indicators**

The main outcome of the study was comparison of the safety and efficacy of GLP-1 receptor agonists (adlyxin) with those of α-glucosidase inhibitor (voglibose) among Chinese people with T2D. The primary endpoint was the number of treatment-emergent adverse events (TEAEs) during 24 months of treatment, while the secondary endpoint was the severity of blood glucose level confirmed by symptomatic hypoglycaemia episodes. These included changes from the baseline values and safety parameters from hematology, biochemistry, calcitonin and pulse rate variables.

**Statistical analysis**

Statistical analysis was carried out using SPSS 21.0 software. All values are expressed as mean ± standard deviation (mean ± SD). One-way analysis of variance (ANOVA) was used for

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multiple comparisons, while Student’s t-test was performed for comparison between two groups. Values of \( p < 0.05 \) were considered statistically significant.

RESULTS

A total of 1250 participants were investigated and given GLP-1 receptor agonist adlyxin (n=500), α-glucosidase inhibitor voglibose (n = 500) or RDs (insulin or acarbose). In the group treated with GLP-1 receptor agonist, there were 25 aborted treatments involving participants who discontinued from the investigation, while 48 α-glucosidase inhibitor users and 18 RD users discontinued during the study period. Adverse events were responsible for the discontinuation. However, baseline characteristics were comparable amongst the three groups (Table 1).

The incidence of TEAEs was highest among the α-glucosidase inhibitor group (87.37 %), followed by GLP-1 receptor agonist group (86.15 %), and least in RD group (70.69 %). These results are shown in Table 2. The GLP-1 receptor agonist users experienced 6.06 % serious adverse events (SAEs) during the secondary safety endpoint. In contrast, users of α-glucosidase inhibitor and and RDs experienced higher SAEs of 8.21 and 7.33 % respectively. There were no fatalities during the study period. In terms of severity, the AEs were mostly mild-to-moderate in many cases. In the case of voglibose users, 5.26 % of the participants discontinued treatment due to AEs, while 8.23 % of adlyxin users discontinued due to AEs (Table 2).

In most cases, gastrointestinal problems were the main reason for the discontinuation of treatment. Diabetic retinopathy was observed among 7.58 % of voglibose users, 5.68 % of adlyxin users, and 6.47 % of RD users (Table 3). There were no specific cases of severe hypoglycemia among all groups. Neoplasms were reported in 7.14, 5.47, and 6.9 % of the patients treated with voglibose, adlyxin, and RD, respectively (Table 3).

In the voglibose treatment group, benign and colorectal cases were most common (8.66 and 4.11 %, respectively), when compared to 3.58 and 2.53 %, respectively, in adlyxin users. With respect to glycaemic control at the end of the study period (24 months), the mean HbA1c (baseline 8.2 %) was significantly reduced in adlyxin (GLP-1 receptor) group, when compared to voglibose (α-glucosidase inhibitor) group. Most of the adlyxin (GLP-1 RA) users were able to achieve the HbA1c target of < 7.0 %. Mean body weight was also significantly decreased in participants treated with adlyxin, when compared to voglibose and reference drug users. Moreover, there were significant reductions in blood pressure among users of adlyxin, when compared to baseline levels. These results are shown on Table 4.

DISCUSSION

In this study, users of adlyxin were able to tolerate overall without any further safety labels. In the primary endpoint, adlyxin users had higher TEAEs than those who used voglibose (α-glucosidase inhibitor) and RDs. However, the occurrence of SAEs was distributed uniformly in the groups. Gastrointestinal adverse events (AEs) were dominant among the GLP-1RAs users, but the symptoms were moderate and mild in many cases, and gradually subsided over time. The AEs also accounted for most of the treatment discontinuations. In fact, gastrointestinal disorders have been reported as common side effects among GLP-1RA users [14,15].

Table 1: Baseline characteristics of the investigated population

| Variable               | \( \alpha \)-Glucosidase inhibitor | GLP-1 receptor agonists | Reference drug |
|------------------------|-----------------------------------|-------------------------|----------------|
|                        | Voglibose n=475                   | Adlyxin n=462           | Insulin, acarbose, etc n=232 |
| Age                    | Mean 62.4 (9.3)                   | Mean 61.8 (9.5)         | Mean 63.1 (9.6) |
| Male/ female (%)       | 68.5/31.5                         | 71.5/28.5               | 70.8/29.2      |
| HbA1c, (mmol/mol)      | 66.3 (10.2)                       | 65.3 (9.8)              | 65.6 (10.4)    |
| HbA1c < %              | 8.2 (1.2)                         | 8.1 (0.9)               | 8.3 (1.3)      |
| FPG (mmol/L)           | 9.0 (1.7)                         | 8.8 (1.8)               | 8.9 (1.8)      |
| FPG (mg/dL)            | 162.7 (29.3)                      | 161.8 (28.1)            | 162.4 (29.9)   |
| Body weight (kg)       | 71.6 (12.4)                       | 68.6 (11.4)             | 72.3 (12.8)    |
| BMI (kg/m²)            | 26.5 (4.3)                        | 26.3 (4.1)              | 26.8 (4.7)     |
| eGFR (mL/min/1.73 m²)  | 102.5 (19.1)                      | 101.2 (18.3)            | 103.4 (20.3)   |
| Physical therapy       | 159 (25.3)                        | 175 (24.1)              | 82 (18.7)      |
Table 2: Incidence of various adverse events observed in the treatment groups

| Variable                             | Voglibose |                       | Adlyxin |                       | Reference drugs |                       |
|--------------------------------------|-----------|-----------------------|---------|-----------------------|-----------------|-----------------------|
| Overview of treatment emergent AEs   | n (%)     | E (%)                 | R (%)   | n (%)                 | E (%)           | R (%)                 |
| Number of participants               | 475       | 921                   | 341.4   | 415                   | 90.48           | 892                   |
|                                      |           |                       |         | 321.4                 | 144             | 164                   |
|                                      |           |                       |         | 70.69                 | 587             | 383.5                 |
|                                      |           |                       |         | 1070                  |                 |                       |
|                                      |           |                       |         | 20(5)                 |                 |                       |
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|                                      |           |                       |         |                       |                 |                       |
|                                      |           |                       |         |                       |                 |                       |
| Death                                | 0 0       | 0 0                   | 0 0     | 0 0                   | 0 0             |                       |
| Serious                              | 39 8.21   | 28 11.3               | 28 6.06 | 17 6.2                | 17 7.33         | 17 8.5                |
| Severe                               | 23 4.84   | 16 5.1                | 8 1.73  | 5 1.6                 | 7 3.02          | 3 1.7                 |
| Moderate                             | 63 13.26  | 51 22.8               | 62 13.42 | 41 16.4            | 31 13.36        | 26 18.3               |
| Mild                                 | 412 86.74 | 945 325.6             | 424 91.77 | 842 289            | 174 75         | 352 196               |
| Leading to premature treatment        | 25 5.26   | 18 6.2                | 38 8.23 | 23 12.5              |               |                       |
| treatment discontinuation            |           |                       |         |                       | 18 7.76       |                       |
| Infections and infestations          | 265 55.79 | 243 87.4              | 219 47.4 | 178 69.4           | 124 53.45      | 175 75.2              |
| Pharyngitis                          | 27 5.68   | 17 4.8                | 21 4.55 | 12 3.8               | 6 2.59         | 8 3.4                 |
| Nasopharyngitis                      | 158 27.48 | 128 46.1              | 148 32.03 | 98 31.4           | 83 35.78       | 76 43.3               |
| Gastrointestinal disorders           | 272 57.26 | 274 89.5              | 267 57.79 | 284 90.2          | 54 23.28       | 53 32.7               |
| Gastroenteritis                      | 31 6.53   | 21 6.7                | 14 3.03 | 11 3.1              | 5 2.16         | 9 2.7                 |
| Nausea                               | 59 12.42  | 43 17                 | 98 21.21 | 54 21.6            | 5 2.16         | 9 1.3                 |
| Constipation                         | 89 18.74  | 49 21.6               | 79 17.1 | 38 13.7             | 12 5.17        | 14 4.3                |
| Abdominal discomfort                 | 32 6.74   | 19 6.1                | 35 7.58 | 16 6.5             | 17 7.33        | – –                   |
| Diarrhoea                            | 48 10.11  | 42 14.7               | 75 16.23 | 34 12.4           | 21 9.05        | 17 4.7                |
| Vomiting                             | 27 5.68   | 22 5.9                | 32 6.93 | 15 4.3             | 6 2.59         | 6 1.7                 |
| Investigations                       | 83 17.47  | 73 18.5               | 119 25.76 | 78 27.7         | 22 9.48        | 18 5.2                |
| Lipase increased                     | 43 9.05   | 32 8.7                | 68 14.72 | 25 8.7          | 8 3.45         | 6 2.1                 |
| Amylase increased                    | 16 3.37   | 14 5                  | 27 5.84 | 9 4.6              | 3 1.29         | 1 1.1                 |

* n = no. of participants; E = no. of events; and R = event rate

Table 3: Characteristics of adverse events based on metabolism and other disorders

| Variable                                      | Voglibose |                       | Adlyxin |                       | Reference Drugs |                       |
|-----------------------------------------------|-----------|-----------------------|---------|-----------------------|-----------------|-----------------------|
| Overview of treatment emergent AEs            | n (%)     | E (%)                 | R (%)   | n (%)                 | E (%)           | R (%)                 |
| Number of participants                        | 475       | 33                    | 11.5    | 71 15.37              | 27 9.5          | 7 3.02                 |
| Metabolism and nutrition disorders            | 49 10.32  | 33                    | 11.5    | 71 15.37              | 27 9.5          | 7 3.02                 |
| Decreased appetite                            | 41 8.63   | 27                    | 9.4     | 59 12.77              | 31 11.2         | 4 1.72                 |
| Diabetic retinopathy                          | 35 7.58   | 16                    | 5.6     | 27 5.68               | 14 4.7          | 15 6.47                |
| Eye disorders                                 | 68 14.32  | 52                    | 19.5    | 75 16.23              | 39 16.4         | 23 9.91                |
| Musculoskeletal and connective tissue disorders | 67 14.11  | 51                    | 17.6    | 87 18.83              | 45 15.8         | 51 21.98               |
| Back pain                                     | 21 4.42   | 15                    | 4.6     | 20 4.33               | 13 3.8          | 24 10.34               |
| Cardiovascular events                         | 3 0.63    | 3                     | 0.8     | 3 0.65                | 2 0.5           | 4 1.72                 |
| Coronary revascularization                    | 1 0.21    | 0                     | 0       | 1 0.22                | 1 0.3           | 2 0.86                 |
| Heart failure                                 | 2 0.42    | 0                     | 0       | 0 0                   | 1 0.43          |                       |
| Benign                                        | 40 8.66   | 19                    | 5.3     | 17 3.58               | 15 4.3          | 8 3.45                 |
| Neoplasms                                     | 33 7.14   | 27                    | 5.1     | 26 5.47               | 17 4.5          | 16 6.9                 |
| colorectal                                    | 19 4.11   | 4                     | 1.6     | 12 2.53               | 3 1.2           | 7 3.02                 |

Severe or BG-confirmed 11 2.38 5 1.1 8 1.68 4 0.9 5 2.16 2 1 symptomatic; *n = number of participants; E = number of events and R = magnitude of event
Table 4: Main outcomes in the groups at the end of the study

| Glycaemia endpoint | α-Glucosidase Inhibitor (Voglibose) | GLP-1 receptor (Adlyxin) | Mean [SD] | Difference from baseline | ETD [95% CI] | P-value | Difference from baseline | ETD [95% CI] | P-value |
|--------------------|------------------------------------|--------------------------|-----------|--------------------------|--------------|---------|--------------------------|--------------|---------|
| HbA1c, mmol/mol    | 65.7 [9.8]                         |                          | 10.68     | −16.5 [0.7]              | −11.4; −9.12 | <.0001 | 23.1 [0.6]               | −18.12; −14.14 | <.0001 |
| HbA1c, (%)         | 8.2 [0.9]                          |                          | −1.4 [0.1] | 24 [−1.15; −1.12]       | <.0001       | 3.5 [0.1] | 76 [−1.61; −1.16]       | <.0001       |        |
| FPG, (mmol/L)      | 8.9 [1.8]                          |                          | −2.6 [0.33]| 13 [−1.82; −1.15]       | <.0001       | 3.8 [0.1] | 14 [−2.61; −2.81]       | <.0001       |        |
| FPG, (mg/dL)       | 162.3 [28.1]                       |                          | −42.3 [1.5]| −29.91                 | <.0001       | 49.0 [1.5] | 36.63                   | <.0001       |        |

Body weight endpoint

| Body weight, (kg) | 70.8 [11.4] | −1.6 [0.4] | 96 [−2.51; −1.12] | <.0001 | 3.6 [0.7] | 82 [−3.12; −2.12] | <.0001 |
| BM (kg/m²)        | 26.5 [4.1]  | −0.9 [0.4] | 10 [−1.05; −0.68] | <.0001 | 1.43 [0.1] | 51 [−1.52; −1.11] | <.0001 |
| Waist circumference (cm) | 89.7 [9.8] | −3.1 [0.6] | 57 [−1.23; −1.14] | <.0001 | 1.6 [0.7] | 51 [−2.14; −1.52] | <.0001 |

There are also various studies with similar reports on treatment discontinuation arising from gastrointestinal AEs [16-18]. The safety of adlyxin (GLP-1 receptor agonists) in the cardiovascular system is of great interest. A study reported similar cardioprotective effect for the GLP-1 receptor agonist semaglutide [19]. In this study, it was observed that adlyxin (GLP-1RAs) was able to achieve significant glycaemic control and BMI index when prescribed as monotherapy or in combination with other RDs. The users of adlyxin experienced a significant cardioprotective effect, when compared to users of other drugs. At the end of the treatment period, most of the participants on adlyxin (GLP-1RAs) were able to achieve the target glycaemic control of the Chinese Diabetes Society target (HbA1c <53.0 mmol/mol) without any further weight gain and symptomatic hypoglycemia. Moreover, the efficacy of adlyxin as regards HbA1c level and BMI was consistent throughout the study period. Similar findings have been reported where the users of GLP-1 receptor agonists showed maintenance of clinically significant glycaemic level and BMI [20,21]. This study also demonstrated the safety profile of GLP-1 receptor agonists over α-glucosidase inhibitor and RDs, based on their glycaemic controls and bodyweight reductions. Therefore, the use of GLP-1 receptor agonist adlyxin is justified among T2D Chinese population as a result of its potential safety profile.

Limitations of the study

The study has certain limitations. First, only a single representative drug of each class of GLP-1 receptor agonists and α-glucosidase inhibitors was considered. Secondly, the sample size was comparatively small. Thirdly, the study was based on only Chinese T2D patients. Thus, the findings may not be accurately applied to non-Chinese populations.

CONCLUSION

This study reveals that the use of the GLP-1 receptor agonist adlyxin significantly reduces HbA1c, bodyweight and BMI, and improves the lipid profile and blood pressure of T2D patients. Adlyxin also produced good and consistent glycaemic control during the entire study period. Besides, there were no safety issues with adlyxin during the study period. Therefore, the GLP-1 receptor agonist adlyxin may be of more potential benefit to Chinese type 2 diabetes population than α-glucosidase inhibitor.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities
pertaining to claims relating to the content of this article will be borne by the authors, all the authors read and approved the manuscript for publication. Qinjin Hu and Jingjing Zhu conceived and designed the study, and analysed the data, draft and wrote the manuscript.

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