Asploro Journal of Biomedical and Clinical Case Reports
(ISSN: 2582-0370)

Commentary

DOI: https://doi.org/10.36502/2024/ASJBCCR.6363

Clinically Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) with Related Factors

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Received date: 15 July 2024; **Accepted date**: 29 July 2024; **Published date**: 05 August 2024

Citation: Bando H. Clinically Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) with Related Factors. Asp Biomed Clin Case Rep. 2024 Aug 05;7(3):201-204.

Abstract

Type 2 diabetes (T2D) is a crucial disease, and glucagon-like peptide 1 receptor agonists (GLP-1RA) have become prevalent as effective oral hypoglycemic agents (OHA). GLP-1RA has clinical effects such as improving glucose variability, reducing weight, and decreasing the risk of cardiovascular disease (CVD). However, recent problems include discontinuation, dropout, and incomplete adherence to GLP-1RA. The discontinuation rates of GLP-1RA were 26.2%, 30.8%, and 36.5% at 3, 6, and 12 months, respectively, and increased to 50.3% for obese patients without T2D. Discontinuation was significantly higher for patients with heart failure (odds ratio 1.09) and CVD (1.08), but not for those with CKD (1.03).

Keywords

Type 2 Diabetes, Glucagon-Like Peptide 1 Receptor Agonists, Oral Hypoglycemic Agent, Proportion of Days Covered, Glucagon-Like Peptide

Abbreviations

T2D: Type 2 Diabetes; GLP-1RA: Glucagon-Like Peptide 1 Receptor Agonists; OHA: Oral Hypoglycemic Agent; PDC: Proportion of Days Covered; GLP-1: Glucagon-Like Peptide

Commentary

Type 2 Diabetes (T2D) has been a crucial disease from medical and social points of view. The treatment for T2D includes oral hypoglycemic agents (OHAs), insulin, and other novel measures. For insulin therapy, several types of insulin and administration methods have been introduced with successful results [1,2]. Furthermore, recent research has brought the development and application of glucagon-like peptide 1 receptor agonists (GLP-1RA) in patients with T2D. Recently, the clinical application of GLP-1RA has expanded to obesity patients in the context of medical and health care [3].

In the real world, the clinical effectiveness of GLP-1RA has been recognized for years [4,5]. Previous investigations have reported various benefits of GLP-1RA, including promoting weight reduction and decreasing the risk of cardiovascular disease (CVD) [6]. However, in actual practice, recent problems

include discontinuation, dropout, and incomplete adherence to these agents [7,8]. The reasons for deprescription for T2D may involve various situations [9]. From an investigation of actual adherence to GLP-1RA, the discontinuation rate for T2D appeared to be approximately 45% within a year after initiation [10].

In the latest report, the adherence to and discontinuation of GLP-1RA have been evaluated for T2D and obesity cases [11]. According to the protocol, the study included 196 thousand participants with an average age of 53.8 years, and a male/female ratio of 58.9%/41.1%. The subjects were aged 18 years or older and received prescriptions for GLP-1RA, including dulaglutide, liraglutide, semaglutide, and exenatide. Discontinuation was defined as no prescription of GLP-1RA for 135 days following every 3-month evaluation from 3 to 12 months. Adherence was defined as the proportion of days covered (PDC), calculated between visits and prescriptions. This research continued from January 2021 to December 2023 for 3 years. Baseline characteristics included clinical manifestations of obesity, T2D, heart failure, chronic kidney disease (CKD), and CVD.

As a result of the current analysis, the discontinuation rates of GLP-1RA were 26.2%, 30.8%, and 36.5% at 3, 6, and 12 months, respectively. By evaluating the obtained rate at 12 months, the discontinuation rate was higher for obesity without T2D among those prescribed GLP-1RA. Specifically, T2D cases showed a discontinuation rate of 35.8%, cases with both T2D and obesity showed 34.2%, while cases with only obesity showed 50.3%, indicating more than half [11].

Furthermore, logistic regression analysis showed that the odds ratio (OR) of discontinuation for obesity-only cases was calculated as 1.79 [95% CI 1.74-1.85] compared to T2D cases, and 0.91 [95% CI 0.89-0.93] for cases with both T2D and obesity. For sex differences, men showed an OR of 1.02. Regarding age influence, younger cases (18-34 years) showed a higher OR than those over 35 years. Other factors for higher discontinuation rates included the presence of gastrointestinal (GI) symptoms (OR 1.04) and higher personal out-of-pocket drug costs (OR 1.02), calculated for every 1% increase. Additionally, discontinuation was significantly higher for patients with heart failure (OR 1.09) and CVD (OR 1.08). In contrast, no significant association was found for CKD patients (OR 1.03). From these data, the reasons for discontinuation of GLP-1RA seem to be related to the purpose of initiation and demographic factors. Further evaluation will be required for the recently progressing prescription of tirzepatide, a new GLP-1RA.

From the results of big data, the real-world situation for GLP-1RA has been clarified. The medical records included 13 million cases from the Clinical Practice Research Datalink in the United Kingdom over 9 years [10]. Related cases were summarized, and several markers were calculated, such as weight changes, discontinuation (prescription gap of more than 3 months), and adherence (PDC of more than 80%). The current evaluation was performed at 1 and 2 years during the study period. Among the big data, 589 cases starting GLP-1RA were detected, with females comprising 56.4% of the sample, a median age of 54 years, and a median BMI of 41.2 kg/m^2. Achievement of a weight reduction of $\geqslant$5% from baseline at 12 and 24 months was 33.4% and 43.5%, respectively. Continuation rates at 12 and 24 months were 64.5% and 59.2%, while discontinuation rates were 45.2% and 64.7%, respectively. From the above, a small proportion of patients starting GLP-1RA could achieve a weight reduction of $\geqslant$5%. This suggests that the actual situation of using GLP-1RA may be less effective than reported in clinical trials. Consequently, various patients treated with GLP-1RA may benefit from additional support measures to improve long-term adherence.

An impressive study was reported [12]. After discontinuation of GLP-1RA treatment for 1 year, weight reduction without treatment was investigated. The research was a post-treatment evaluation extension of a randomized, controlled trial (RCT) in Copenhagen. Adult cases with obesity (BMI 32-43 kg/m^2, aged 18-65 years) had completed an 8-week low-calorie diet associated with a 13.1 kg weight reduction (0-8 weeks). Subsequently, a maintenance project (0-52 weeks) included 4 groups randomly allocated (1:1:1:1) with/without supervised exercise and with/without GLP-1RA. A total of 166 cases completed the protocol. For cases of GLP-1RA termination at 1

year, weight regain was +6.0 kg for 52-104 weeks. If supervised exercise was added, weight regain was 2.5 kg. When combined treatment (GLP-1RA and exercise) continued for 0-104 weeks, the results showed -5.1 kg for weight and -2.3% in body fat percentage, compared with termination of GLP-1RA alone.

From recent research developments, the difference between endogenous GLP-1 and alternatives for GLP-1RA has been a focus [13]. The medical agent GLP-1RA has shown various beneficial mechanisms for humans, including weight reduction, decreased blood glucose/HbA1c, and reduced cardiovascular risk. Although this clinical efficacy appears similar, increasing evidence suggests that these agents may differ from endogenous GLP-1 regarding their action routes. Considering the limitations of GLP-1RA, the development of agents that stimulate GLP-1 release could be explored. These functions and mechanisms will become an important discussion in the future.

In summary, some perspectives on GLP-1RA discontinuation during treatment have been described in this article. Future research development is expected for the prevalent use of GLP-1RA in clinical practice.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

Funding

There was no funding received for this paper.

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