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Latest Topics on Pharmacotherapy for Obesity Including Glucagon Like Peptide-1receptor Agonists (GLP-1RAs)

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Abstract

Obesity has been crucial diseases. Several agents have been used including Phentermine, Mazindol, Orlistat, Phentermine/Topiramate, Naltrexone/Bupropion and Liraglutide from 1959 to present. Glucagon like peptide-1receptor agonists (GLP-1RAs) has been used for type 2 diabetes mellitus (T2DM). As GLP-1RA, liraglutide is given 0.9 mg/day for T2DM, and 3.0 mg/day for obesity. Similary, semaglutide is given 1.0 mg/week for T2DM and 2.4 mg/week for obesity. Semaglutide brought 14.9% weight reduction for 68 weeks. There is a novel combination of GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) for treating obesity, which achieved at least 10% weight reduction in 6-39% of cases for 26 weeks.

Keywords: ***Obesity; Liraglutide; Semaglutide; Glucagon like peptide-1receptor agonists (GLP-1RAs); Glucose-dependent insulinotropic polypeptide (GIP)***

For decades, metabolic syndrome and locomotive syndrome have become major medical and social problems in developed and developing countries. Among them, obesity seems to be the fundamental cause of those illnesses. Several standard treatments are used for obesity, such as diet, exercise, and behavioral therapies so far. Intervention for the lifestyles would be indispensable. Some surgery methods may be performed when the case is estimated to be necessary [1].

However, pharmacotherapy for obesity has been more frequent for long. From historical point of view, several kinds of agents for obesity have been developed [2]. Among them, some agents have been used until now, which are Phentermine, Mazindol, Orlistat, Phentermine/Topiramate, Naltrexone/Bupropion and Liraglutide from 1959 to present [3]. In this article, recent perspectives and topics concerning some medical agents for obesity would be described with up-to-date medical information.

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As regards to anti-obesity medicine, there are some agents that are particularly expected in recent years [4]. They are glucagon like peptide-1receptor agonists (GLP-1RAs), which were expected to have an insulin secretagogue action from pancreatic β cells as an incretin-related drug [5]. When liraglutide is provided, starting dose is 0.3mg/day, followed by usual maintenance dose 0.9 mg/day and maximum dose 1.8 mg/day. After lots of clinical experiences of liraglutide, the effect of suppressing appetite was widely known, that is via GLP-1 receptors expressed in the central nervous system such as the hypothalamus [6]. As a result, liraglutide (Saxenda R) has been approved in the United States as an anti-obesity drug with a maximum dose of 3.0 mg and has already been launched [7].

Similarly, there has been semaglutide as one of GLP-1RAs for diabetes. It starts with a 0.25 mg injection once per week, maintains usually at 0.5 mg/week, and increases up to 1.0 mg/week when needed. As to the indication for obesity, clinical study of semaglutide has been conducted with a maximum dose of 2.4 mg/week. In particular, the effect of weight reduction was observed 14.9% for 68-week period. Simultaneously, the control group showed 2.4% reduction [8]. Then, the difference is calculated to be 12.5%. Consequently, it is expected that this will be applied in the actual practice for the near future [9].

LY3298176 has been a novel combination of GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) [10]. It was developed for the purpose of treatment of T2DM. The effect and safety of these agents were studied for poor controlled T2DM. The study included 316 cases for 6 treatment groups, which are LY3298176 (1, 5, 10, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. As a result, LY3298176 showed HbA1c reduction as -1.06%, -1.73%, -1.89%, -1.94% for 1 mg, 5 mg, 10 mg, 15 mg, respectively. Furthermore, it showed compared difference data to dulaglutide of HbA1c as -0.15%, -0.52%, -0.67%, -0.73%, for 1 mg, 5 mg, 10 mg, 15 mg, respectively. Regarding weight changes, 14%-71% of cases in group LY3298176 achieved at least 5% reduction (vs 22% with dulaglutide, 0% with placebo) and 6%-39% achieved at least 10% reduction (vs 9% with dulaglutide, 0% with placebo). Consequently, dual GIP and GLP-1RA (LY3298176) showed significantly higher effect for glucose variability and weight reduction than dulaglutide. It was associated with an acceptable safety and tolerability profile [11]. This agent will develop a new therapeutic option for T2DM.

As options for weight control, two agents were known. They are GLP-1RA, semaglutide and a long-acting amylin analogue, Cagrilintide [12]. The study was conducted for the purpose of combined administration of these agents in the light of pharmacokinetics, tolerability and safety. The methods included the assignment of subcutaneous cagrilintide (6 different doses: 0.16, 0.30, 0.60, 1.2, 2.4, 4.5 mg) once-weekly for 20 weeks, associated with semaglutide 2.4 mg. As a result, the mean weight reduction was -7.4% for combined semaglutide 2.4 mg and cagrilintide 4.5 mg. This concomitant therapy showed safety and toleration. Future trials and research will be expected for the combination of these agents.

What kind of mechanism does GLP-1RA work in the light of neurology and gastroenterology? After subcutaneous administration, GLP-1RA is thought to reach the central nervous system (CNS) directly or act on the appetite center of the hypothalamus via the vagal afferents [13]. It is known that it suppresses appetite and increases energy consumption, and also acts on gastrointestinal motility such as the medulla oblongata terminal area and the center of nausea and vomiting. Among these, it is not clarified the extent to which the action in the medulla oblongata terminal area has anti-obesity effect. As a matter of fact, however, the important point is how much the reverse effects related to the gastrointestinal tract can be reduced. Consequently, GLP-1RA can bring weight reduction and influence neural activities of energy expenditure, reward

and food intake [13]. GLP-1RA is known to induce dietary patterns that repel high-fat diets [14]. From this point of view, progress in research is expected for the future changes in dietary preferences.

As described above, the development of anti-obesity agents has been currently a large boom worldwide for targeting gastrointestinal hormones and their receptors. Furthermore, glucagon [15], cholecystokinin (CCK) [16], peptide YY (PYY) [17], growth differentiation factor 15 (GDF-15) [18], and other agents can enhance the signal of appetite-suppressing hormones. Research developments are found concerning the hormone “ghrelin” that can promote appetite. One is the agent that reduce the action of ghrelin, and another is the agent that enhance the action of ghrelin inhibitor liver-expressed antimicrobial peptide 2 (LEAP-2) [19].

In summary, there has been a history of hardship for treating obesity for long [2,3]. Starting the injectable treatment of GLP-1RA in clinical practice, there is no doubt that pharmacotherapy in this area has entered a new era. As this agent becomes one of the triggers, international basic, clinical, and translational medical research will be brought together and developed. Continuing various research, it is expected that pharmacotherapy for life-threatening obesity will be developed adequately in the future.

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