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Review Article

Survodutide, a promising agent with novel mechanism of action for treatment of obesity and type 2 diabetes

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Abstract

Activation of the glucagon-like peptide-1 receptor (GLP-1R) and glucagon receptor (GCGR) may result in synergistic effects on glycemic control and weight reduction. Survodutide is a dual agonist of GLP-1R and GCGR under development for treatment of type 2 diabetes, obesity and non-alcoholic steatohepatitis (NASH). In a phase 2 trial of 16-week duration including patients with type 2 diabetes, subcutaneous survodutide given once weekly reduced glycated hemoglobin (HbA1c) levels by 1.5% versus placebo, which was comparable to the reduction achieved by semaglutide (1.0 mg/w). In another phase 2 trial of obese subjects without diabetes, percent weight loss with the highest dose of survodutide was 12.1% versus placebo and did not reach a plateau up to the end of follow-up at 46 weeks. Use of survodutide was associated with significant reduction in systolic and diastolic blood pressure and plasma triglycerides. The most common adverse effects of survodutide were gastrointestinal (GI) disorders reported by 55% of patients (versus 22% with placebo) in the diabetes trial and by 75% (versus 42% with placebo) in the obesity trial. Drug discontinuation rates were 16-25% with survodutide, 4% with semaglutide and 4-5% with placebo. Results of a phase 2 trial including patients with NASH are pending. The major limitation of survodutide is suboptimal tolerability due to GI adverse effects attributed in part to rapid dose escalation. Overall, survodutide is a promising candidate drug with a novel mechanism of action for treatment of type 2 diabetes and obesity. Phase 3 clinical trials, with slower dose titration of survodutide should clarify its efficacy and safety in a broader population of patients with type 2 diabetes, obesity and NASH.

Key words: survodutide; diabetes; obesity; safety; dual GLP-1/GCGR agonists; non-alcoholic steatohepatitis

Introduction

The naturally occurring hormone oxyntomodulin is a weak agonist of GLP-1R and GCGR and was found to decrease body weight and blood glucose [1]. However, the therapeutic use of oxyntomodulin was hampered by its short half-life [1]. Survodutide (code BI 456906) is a synthetic 29-amino-acid peptide derived from glucagon and incorporating amino acid residues from GLP-1 [2]. As result of albumin binding through a C18 diacid, survodutide has extended terminal half-life of 109-115 h making it suitable for once-weekly subcutaneous administration [3,4]. Contrary to oxyntomodulin, survodutide is resistant to the enzymatic degradation by the dipeptidyl peptidase-4 [3]. Weight loss is mediated by both GLP-1 and GCGR. Activation of GCGR causes increased energy expenditure, whereas activation of GLP-1 R results in decreased food intake through central receptors in hypothalamus and hind brain [2]. In addition, activation of GLP-1R controls postprandial hyperglycemia via stimulation of insulin secretion and delay of gastric emptying [2]. It should be emphasized that survodutide activates GLP-1R more actively than GCGR with a ratio of approximately 8:1 [3]. The idea behind this balanced receptor agonism of survodutide is to provide weight loss through stimulation of both GCGR and GLP-1 R while controlling hyperglycemia through the GLP-1R [3]. Thus, whereas glucagon may cause hyperglycemia, the greater activation of GLP-1R versus GCGR by survodutide leads to weight reduction without exacerbation of glycemic control [2]. Cotadutide (code MEDI0382) is a another dual GCGR and GLP-1R agonist under development with an agonistic activity of 5:1 ratio [5]. However, data regarding treatment of diabetes and obesity by cotabutide are more limited and less encouraging compared with survodutide [6]. Two phase 2 clinical trials were recently published to evaluate efficacy and safety of survodutide in obesity and type 2 diabetes [7,8]. Therefore, this article will focus on critical appraisal of survodutide as new therapy for type 2 diabetes and obesity based on available data.

Survodutide for treatment of type 2 diabetes

In patients with type 2 diabetes, different doses of survodutide (0.3, 0.9, 1.8, 2.7 mg once weekly, and 1.2 mg and 1.8 mg twice weekly) were compared in a randomized, partly double-blind, phase 2 trial, with open-label semaglutide 1.0 mg once weekly and placebo [7]. Patients [n=411, 44% women, mean age 57.3 years, mean body mass index (BMI) 33.9 kg/m^2, mean HbA1c 8.1%] were randomized into groups of approximately 50 subjects (except placebo group n=59). All patients were receiving metformin [7]. Primary endpoint was the change in HbA1c levels from baseline to 16 weeks [7]. With the smallest dose of survodutide (0.3 mg/week), mean reductions in HbA1c values were 0.9% but ranged from 1.5 to 1.7% with higher survodutide doses without clear dose-related response [7]. The decrease in HbA1c values in the survodutide groups (except the lowest dose) was similar to the 1.5% HbA1c reduction achieved in the semaglutide group [7]. Reduction of HbA1c levels in the placebo group was minimal approximately 0.2% [7]. Inspection of curves of HbA1c changes with time suggest that decreases in HbA1c values reached a plateau at 16 weeks with survodutide, but not with semaglutide [7]. However, longer duration of therapy is needed to confirm this finding.

Survodutide for treatment of obesity

A second randomized, double-blind phase 2 trial examined effects of survodutide on weight loss in obese subjects without diabetes [8]. Subjects (n=384, 68% women, mean age 49 years, mean BMI 37.1 kg/m^2, mean weight 105.7 kg) were randomized to survodutide weekly doses of 0.6 mg, 2.4 mg, 3.6 mg, 4.8 mg or placebo in addition to dietary and physical activity counselling [8]. The trial was composed of 2 phases: an initial 20-week dose escalation phase and 26 week-dose maintenance phase [8]. At 46 weeks, mean percentage weight loss from baseline, the primary endpoint, ranged from 6.2% (95% CI 8.3 to 4.1) with survodutide 0.6 mg to 14.9% (95% CI, 16.9 to 13.0) with survodutide 2.4 mg versus 2.8% (95% CI, 4.9 to 0.7) with placebo [8]. Weight loss of ≥10%, a secondary endpoint, was achieved by 69% of subjects with survodutide 4.8 mg compared with 11% with placebo [8]. In the diabetes study of Bluher et al [7], weight reduction was a secondary endpoint. After 16 weeks, survodutide 1.8 mg/w was associated with mean relative weight reduction of 8.7% (95% CI, 10.1 to 7.3) [7]. Weight loss with survodutide doses ≥ 1.8 mg/w was significantly greater than the 5.3% (95% CI, 6.6 to 4.1) weight reduction achieved by semaglutide [7]. In the 2 trials, the decrease in weight by survodutide was progressive up to the end of intervention without evidence of reaching a plateau [7,8].

Effects of survodutide of cardiovascular risk factors

Compared with placebo, survodutide 3.6 mg/w was associated with significant reduction of systolic blood pressure and diastolic blood pressure by 6.2 mmHg and 2.9 mmHg, respectively [8]. In addition, there were significant reductions in plasma concentrations of triglycerides and very low-density lipoprotein cholesterol (VLDL-C) by approximately 28% with the 2.4 mg and 3.6 mg doses of survodutide compared with an increase of 5% with placebo [8]. No significant effects were observed with survoditide on other plasma lipids [8].

Effects of survodutide on plasma markers of fatty liver

Given its effects on weight loss and possible stimulation of fatty acid oxidation in the liver through glucagon agonism [2], there was interest to explore the effects of survodutide for management of NASH [2]. Survodutide treatment led to amelioration of some markers of NASH such as enhanced liver fibrosis score and pro-C3. However, there were no significant effects on NASH-related Fib-4 score, aspartate aminotransferase/platelet ratio and non-alcoholic fatty liver disease (NAFLD) score [7].

Safety of survodutide

In the phase 1 studies conducted by Jungnik et al [9], the commonest drug-related adverse effect of survodutide was decreased appetite reported by 50% of healthy subjects. However, in phase 2 studies, decreased appetite occurred in 16.6% of subjects with obesity versus 3.4% with placebo [7]. In fact, in the diabetes trial, survodutide had minor and inconsistent effects on hunger [7]. In phase 2 trials, the most frequently reported adverse effects of survodutide were GI disorders, namely nausea, vomiting, diarrhea, constipation and dyspepsia [7,8]. In the diabetes trial, GI disorders were reported by 55%, 28%, 22% of patients randomized to survodutide, semaglutide, and placebo, respectively [7]. In the obesity trial, such disorders were reported by 75% and 42% in the survodutide and placebo, respectively [8]. No increase in incidence of serious adverse was observed with survodutide compared with placebo [7,8]. Yet, dehydration and subsequent renal failure in 2 subjects and one case of angioedema were reported in the obesity study [8]. Adverse effects leading to treatment discontinuation occurred in 15.9% of patients with type 2 diabetes receiving survodutide, 5.1% with placebo and 4.0% with semaglutide [7]. In the study of obese subjects, discontinuation rates were 25% and 4% with survodutide and placebo, respectively [8]. Most of the discontinuations occurred initially in the first 6 weeks of the study during drug titration phase and were mainly attributed to GI disorders.

Effect of survodutide on heart rate

Survodutide was associated with increase in heart rate; the mean increase across survodutide doses being 2.3-7.3 beats per minute (bpm) versus 5.9 bpm with semaglutide and 1.7 bpm with placebo [7]. The increase in heart rate may be mediated by the GLP-1R and GCGR in the sinoatrial node of the heart [10,11]. Meanwhile, no increase in tachy-arrhythmias or cardiovascular events was reported with the use of survodutide [7-9].

Survodutide versus cotadutide

Available limited data suggests that the once daily cotadutide may be less effective than survodutide (table 1). Thus, in the only relatively large (n=834) phase 2b trial of cotadutide, placebo-corrected reduction in HbA1c levels was 0.74% and percent weight loss was 4.3% at 54 weeks [6]. However, comparison data should be interpretated with great caution because no direct comparison is available between these 2 dual GCGR and GLP-1R agonists. With the use of both agents, rates of GI adverse effects were elevated and exceeded rates in subjects randomized to the GLP-1R monoagonists liraglutide (1.8 mg/w) and semaglutide (1.0 mg/w) [6,7].

	Survodutide [7,8]	**Cotadutide [6]**
Frequency of subcutaneous of administration	Once weekly	Once daily
GLP-1R to GCGR agonist activity ratio	8:1	5:1
Maximum hemoglobin A1c reduction vs placebo	1.5% at 16 weeks	weeks 0.74% at 54 weeks
Maximum percent weight reduction vs placebo	12.1% at 46 weeks	4.3% at 54 weeks
Maximum percent reduction in plasma triglycerides	33% at 46 weeks	12% at 54 weeks
Frequency of gastrointestinal adverse effects	High	High

Table 1: Comparison between survodutide and cotadutide

Advantages of survodutide

Survodutide was effective in both lowering HbA1c levels by approximately 1.5-1.7% in patients with type 2 diabetes and body weight by approximately 12% in subjects with obesity [7,8]. Thus, as anti-diabetic agent, survodutide was similar in efficacy to submaximal doses of semaglutide 1.0 mg/w [7]. It is possible that semaglutide in its maximal doses of 2.4 mg/w prove more effective than survodutide in terms of glycemic control. Meanwhile, with respect to effects on weight, survodutide was more effective in reducing weight compared with semaglutide 1.0 mg/wk, 6.6% and 5.3% reduction, respectively [7]. Again, these results may change if the comparison was done with the highest semaglutide dose of 2.4 mg/w. The decrease in blood pressure and plasma triglycerides represent other advantages of survodutide, which are likely the result of weight loss [8]. Injection sites reactions were not reported with survodutide administration [7,8].

Limitations of survodutide

Survodutide has important limitations. First, the high rates of GI disorders and discontinuation rates reaching 25-29% (versus 4% with placebo) is concerning [8]. However, rapid escalation of survodutide dose every 2 weeks may be a contributing to these high rates of GI adverse effects [8]. Second, for unclear reasons, women respond better than men in terms of weight loss induced by GLP-1 based drugs [12,13]. Therefore, the weight loss effect of survodutide may be inflated in the obesity trial that included 68% women [8]. Third, while head-to-head comparison is not available, survodutide seems less effective than retatrutide, the tri-agonist of GLP-1R, GCGR in addition to receptors of gastric inhibitory polypeptide (GIP) [12]. Thus, in a phase 2 obesity trial including subjects with similar baseline age, weight, but only 48% women, placebo-corrected weight reduction achieved by once-weekly retatrutide was approximately 22% after 48 weeks [12]. Fourth, most subjects (78-83%) in whom survodutide was evaluated were Whites [7,8].

Conclusions and current directions

Survodutide is a promising agent pertaining to a novel class of dual GLP-1 and GCGR agonists. Results from phase 2 trials in type 2 diabetes and obesity lasting up to 46 weeks suggest that the drug is effective in reducing weight and HbA1c levels [7,8]. Increased prevalence of GI disorders represents the major limitation of survodutide [7,8]. Phase 3 trials under the name of SYNCHRONIZE Program are underway to evaluate long-term efficacy and safety of survodutide in a wider subject population. The relatively long duration of these trials will allow slow up-titration of survodutide dose to diminish its GI adverse effects. Survodutide is also being evaluated in a phase 2 study for treatment of NASH based on its beneficial effects on weight, glycemic control, and potential increase in hepatic lipid oxidation via the GCGR [2,14]. The effects of survodutide on mortality and cardiovascular events will be evaluated in the SYNCHRONIZE-CVOT trial including 4935 patients with high cardiovascular risk with a planned follow-up duration of up to 2 years and 3 months [15]. Results of the above studies should clarify the safety and efficacy of survodutide. In the meantime, other dual GLP-1R and GCGR agonists are under development, e.g. pemvidutide and the oxyntomodulin analogue mazdutide [16]. The different agonistic GLP-1R/GCGR ratios of these new drugs will allow the selection of the most effective and safest agents for management of obesity, type 2 diabetes, and NASH.

Conflict of interest: the authors do not conflict of interest to declare.

Abbreviations: GLP-1R: glucagon-like peptide-1 receptor. GCGR: glucagon receptor

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