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Spotlight

Antagonizing GIPR adds fire to the GLP-1R flame

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Unimolecular co-agonists at the GLP-1/GIP receptors have recently achieved remarkable anti-obesogenic feats; yet, in a recent Phase 1 clinical trial, Véniant and colleagues report astounding body-weight loss, and an appreciable safety profile, in participants with obesity using the GLP-1R agonist/GIPR antagonist AMG 133.

Tackling obesity through novel pharmacology

Anti-obesity pharmacotherapies have gained global attention due to the heightened risks of cardiovascular, gastrointestinal, and endocrine conditions associated with obesity. Pharmacological intervention is the favored scalable solution to meet the increasing demand for weight reduction in comparison to the invasive yet highly effective bariatric surgery, which itself is often accompanied by anti-obesity pharmacology. The anti-obesity renaissance began with the pivotal introduction of long-acting agonists at the glucagon-like peptide 1 receptor (GLP-1R), such as once-daily liraglutide and once-weekly semaglutide, both of which are well-known for decreasing body weight via centrally mediated inhibition of food intake. Preceding its approval for the treatment of obesity in the USA in 2021, Wegovy® (semaglutide 2.4 mg) demonstrated an average 14.9% body weight reduction in non-diabetic individuals who were overweight or obese over the course of 68 weeks in the STEP 1 clinical trial, with 6% of the reduction occurring by week 12 (Figure 1) [1]. Meanwhile, research into mono-agonists at the glucose-dependent insulinotropic polypeptide receptor (GIPR) initially lagged behind due to their limited insulinotropic and body weight-lowering efficacy within the context of diabetes. However, identified synergy between GLP-1 and GIP co-administration on body weight reduction led to the development of the first unimolecular GLP-1/GIP dual-agonist in 2013 by Richard DiMarchi and Matthias Tschöp [2]. This approach was further refined into the GLP-1/GIP dual-agonist tirzepatide, which was approved for the treatment of obesity in the USA in 2023 as Zepbound® (tirzepatide 2.5–15 mg). In the SURMOUNT-1 Phase 3 clinical trial, tirzepatide demonstrated remarkable body weight reductions of 22.5% over the course of 72 weeks in non-diabetic patients with obesity, with approximately 8% body weight reduction achieved by week 12 (Figure 1) [3]. Additionally, retatrutide, a GLP-1/GIP/glucagon triple agonist largely considered to possess the greatest acute body weight-lowering capacity, achieved 24% body weight reduction in just 48 weeks in non-diabetic individuals with obesity, with approximately 12% weight loss occurring by week 12 (Figure 1) [4]. Despite the success of GIPR co-agonism in anti-obesity pharmacology, paradoxical success of GIPR antagonism has taken root. In an exciting recent study by Véniant *et al.*, a novel approach featuring an antibody-based GIPR antagonist conjugated to two GLP-1 peptides, known as AMG 133, achieved approximately 14.5% body weight reduction at 12 weeks in a Phase 1 clinical trial in non-diabetic individuals with obesity [5].

AMG 133: Phase 1 clinical trial in participants with obesity

AMG 133 is a fully potent human GIPR-specific monoclonal antibody (GIPRab) conjugated to two modified GLP-1 peptides at diametrically opposed positions on the heavy chains of an Fc fragment. Its optimization arises from earlier GLP-1/GIPRab iterations directed toward maximal GLP-1R efficacy, potent GIPR antagonism, and efficacious body weight reduction in obese nonhuman primates [5,6]. Following successful preclinical evaluations, the first Phase 1 clinical trial featuring AMG 133 in participants with obesity started in the USA to assess both safety and efficacy via single and multiple ascending dose (SAD/MAD) trials. In the SAD trial, 49 participants were given one subcutaneous injection of either placebo or one-of-six AMG 133 doses between 21 mg and 840 mg. Participants experienced only mild adverse gastrointestinal events most frequently characterized by nausea, vomiting, and dyspepsia, which is not unlike other GLP-1R-centric agonists even as the highest dose of AMG 133 (840 mg) contains a proportionate 35 mg of active GLP-1R agonist. The 840 mg treated group achieved appreciable weight reduction of ~8% by day 150 post-injection. With the 23-day half-life of the molecule and the lowest 21 mg dose mirroring weight loss of 840 mg within the first 15 days post-treatment, these results at day 150 likely originate from therapeutically relevant amounts of residual circulating drug. In the MAD trial, 26 participants with obesity were given either placebo, 140 mg, 280 mg, or 420 mg in three subcutaneous injections separated by 4 weeks each. Each dosage group exhibited gastrointestinal adverse events, predominantly characterized as mild nausea and vomiting. Notably, the 420 mg AMG 133 treatment reduced body weight by ~14% 30 days after the final subcutaneous injection (study day 85). This outcome was accompanied by early transient alterations in fasting free fatty acids, and significant/near-significant decreases in circulating glucose, glucagon, and high-sensitivity C-reactive protein. Together, AMG 133 appears to possess a favorable safety profile, and may be one of the most metabolically efficacious agents for obesity treatment to date; however, qualitative comparison to drugs such as semaglutide and tirzepatide warrants further information

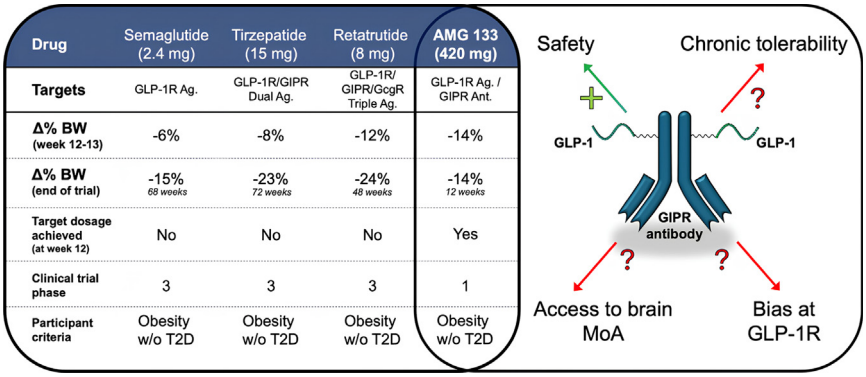

Figure 1. Contextual perspective of the Phase 1 AMG 133 trial in patients with obesity. (Left) Unifying overview between Phase 3 clinical trial body weight (BW) outcomes in patients with obesity given the glucagon-like peptide 1 receptor (GLP-1R) mono-agonist semaglutide, GLP-1R/glucose-dependent insulinotropic polypeptide receptor (GIPR) dual-agonist tirzepatide, or GLP-1R/GIPR/GcgR triple-agonist retatrutide, relative to the Phase 1 clinical trial results of GLP-1R agonist/GIPR antagonist AMG 133. (Right) Open questions pertaining to the characterization of AMG 133, some of which have been answered in the current Phase 1 clinical trial (green) [5], and those which remain for future preclinical and clinical research (red). Abbreviations: MoA, mechanism of action; T2D, type 2 diabetes mellitus.

on drug performance in subsequent clinical trials.

Questions that continue to unravel…

The biological dynamics that allow both GIPR co-agonism and complimentary antagonism to synergize with GLP-1R agonism for similar body weight loss remain enigmatic, nonetheless the superior effectiveness of both is undisputed [3,5,7].

To agonize or antagonize GIPR within GLP-1R co-agonism for body weight?

GIPR agonism primarily triggers weight loss by targeting central nervous system feeding centers, particularly GIPR$^+$ GABAergic neurons in the hindbrain and arcuate nucleus (ARC) [7,8]. These targets also enable GIPR agonism to ameliorate nausea, a common adverse effect of GLP-1R agonism and chemotherapies [7]. This anti-nausea effect potentially allows for higher dosing of the GLP-1R component of tirzepatide (2.5–15 mg) relative to the GLP-1R mono-agonist semaglutide (2.4 mg), possibly contributing to the superiority of tirzepatide on body weight loss. Despite lack of severe nausea by AMG 133 within this current Phase 1 clinical trial, questions remain as to how long-term GIPR complimentary antagonism with GLP-1R agonism will influence tolerability.

Regarding metabolic endpoints, GIPR antagonism in peripheral adipocytes is reported to inhibit GIP-stimulated lipid uptake and lipogenesis [9]. This antagonistic approach has presented therapeutic opportunity to limit fat mass gain without clearly affecting food intake, and thus partly underlies conceptual development behind the first GLP-1/hGIPRab [10]. However, in obese non-human primates, the superior weight reduction achieved by GLP-1/hGIPRab over GLP-1R mono-agonists is predominantly due to synergistic food intake suppression [5,6,10]. This raises the question: how does GLP-1R agonism/GIPR antagonism synergistically reduce food intake?

AMG 133 in the brain?

Antibody access to the brain is controversial, with most evidence suggesting limited transport, if any. It is generally acknowledged that the potent suppression of food intake by GLP-1R agonism is mediated by central GLP-1R$^+$ neurons in the ARC [7]. Interestingly, GIPRab administration alone does not effectively reduce food intake to a degree that leads to net body weight loss in obese animals, potentially due to limited central access [6,9,10]. Therefore, the body weight loss induced by AMG 133 via synergistic food intake suppression is likely through central GLP-1R signaling and an unknown GIPR mechanism. A crucial question arises: does AMG 133 still gain access to central GLP-1R$^+$ neurons – and if so, does this central access route also grant conjugated GIPRab localization into the same central feeding region? Alternatively, does peripheral GIPR antagonism explain the metabolic synergies of AMG 133, as synergistic body weight loss is also retained within loose combination of liraglutide and GIPRab [10]?

Replicating GIPR functional desensitization or antagonizing GIPR$^+$ GABAergic systems?

Chronic GIPR agonism has been suggested to desensitize this receptor, leading to a paradoxical antagonistic effect. This 'antagonistic' effect, whether achieved through chronic agonism or direct antagonism of the GIPR, is hypothesized to mimic the protective anti-obesogenic effect observed in global GIPR knockout mice. This mimicking hypothesis has been fundamental in the strategic composition of AMG 133 [6]. However, while knockout of GIPR in GABAergic neurons selectively recapitulates shielding against diet-induced obesity (DIO), weight loss mediated by GIPR agonism also paradoxically requires GIPR$^+$ GABAergic neurons. Thus, two opposing approaches converge on the same neural population to promote lower body weight [8]. This brings the question: does antagonism of GIPR$^+$ GABAergic neurons mimic the effects of GABAergic GIPR neuronal knockout? If so, is the enhanced body weight loss seen with tirzepatide and AMG 133 therefore attributable to functional desensitization and direct antagonism of GABAergic GIPR, respectively? Addressing this challenge is complicated by the fact that chronic GLP-1R agonism also desensitizes the GLP-1R in various cell types [7], and that a degree

of DIO protection is also observed during GLP-1R signal inhibition [11]. These data caution against extrapolating genetic model phenotypes to drug candidate mechanisms.

Is AMG 133 a biased GLP-1R agonist?

Questions have arisen regarding the mechanism driving the superior body weight reduction of tirzepatide relative to the GLP-1R mono-agonist semaglutide. A focus centers on whether this superiority results from parallel GLP-1R/GIPR signaling, or from biased signaling, where tirzepatide engages GLP-1R downstream dynamics differently from semaglutide. *In vitro* characterization relative to GLP-1 at the GLP-1R indicates AMG 133 as having cAMP and receptor internalization dynamics similar to tirzepatide [6,7]. While further methodologies may be needed to better understand the intracellular GLP-1R dynamics of AMG 133, comparative enhancements in body weight-lowering effect by other GLP-1R mono-agonists are suggested to be attributable to biases or partial agonism at the GLP-1R [12]. Therefore, do the differing signaling and trafficking dynamics of the GLP-1R by AMG 133 influence its body weight-lowering capacity?

Concluding remarks

In summary, AMG 133 offers a novel approach to maximizing body weight reduction by agonizing the GLP-1R with concurrent antibody-based GIPR antagonism. Promising preclinical experiments in obese animals have further been supported by Phase 1 clinical trial results in humans with obesity, confirming the potency of AMG 133 for clinical weight reductions, without toxicity or severe adverse gastrointestinal events. Thus, the future is bright for new approaches to anti-obesity therapy, with AMG 133 presenting a highly novel strategy that leverages the enigmatic nature of the GIPR.

Declaration of interests

None declared by authors.

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