Bridging therapeutic areas in the evolving metabolic space: opportunities, challenges and future perspectives

The metabolic space is one of the fastest growing areas of research, with recent breakthroughs paving the way for rapid expansion – but what prompted these advancements and will they continue?

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Introduction

Since the abatement of the COVID-19 pandemic, healthcare has witnessed an explosion in the numbers of all phases of clinical trials using glucagon-like peptide-1 receptor agonist (GLP-1RA) therapies (Figure 1). This article will explore what are the key drivers of this growth and what new challenges does this rapidly changing landscape pose for the clinical research industry?

Three key drivers of growth of GLP-1 research

Multiple beneficial outcomes of GLP-1s have expanded their indications

The beneficial effects of GLP-1s on multiple clinical outcomes have expanded their indications beyond glycaemic endpoints of type 2 diabetes mellitus (T2DM). The proven safety and efficacy of GLP-1s in persons with diabetes now extends to cardiovascular disease (CVD), chronic kidney disease (CKD) and obesity. Moreover, their unique glucose-dependent stimulation of insulin secretion and the consequent low hypoglycaemic risk has permitted the exploration of GLP-1s' efficacy in non-diabetic populations.

Besides the incretin effect (whereby oral glucose elicits higher insulin secretory responses than intravenous glucose), preclinical studies have shown that GLP-1s also confer a neuroprotective and anti-inflammatory effect, which has spawned a new realm of GLP-1 research into neurodegenerative disease. Clinical research into new indications for GLP-1-based therapies has now been expanded beyond the metabolic realm to include Alzheimer's disease, Parkinson's disease, multiple sclerosis, alcohol abuse with comorbid obesity and sepsis, and others.

It is, however, the breakthrough in the treatment of obesity that stands out as the key therapeutic indication that is driving the growth in GLP-1RA drug development.

GLP-1RA-based single molecule multi-agonists

The combined effect of multi-agonists that target GLP-1, glucagon and glucose-dependent insulinotropic polypeptide (GIP) receptors has produced a new range of potential pharmacotherapies. Due to their differential and balanced mechanisms (biased agonism), multi-agonists may be able overcome the limitations of single hormones. Biased agonism has the potential to reduce side effects such as nausea whilst maintaining or enhancing therapeutic efficacy and reducing tachyphylaxis.[2]

These GLP-1RA-based multimolecular combinations promise mechanistic benefits for the management of T2DM, obesity and/or metabolic dysfunction-associated fatty liver disease (MAFLD), and the range of novel combinations continues to proliferate. Other therapies in early development include GLP-1RAs+FXR agonist+ACC inhibitor or GLP-1RAs+FGF-21 receptor agonist for metabolic

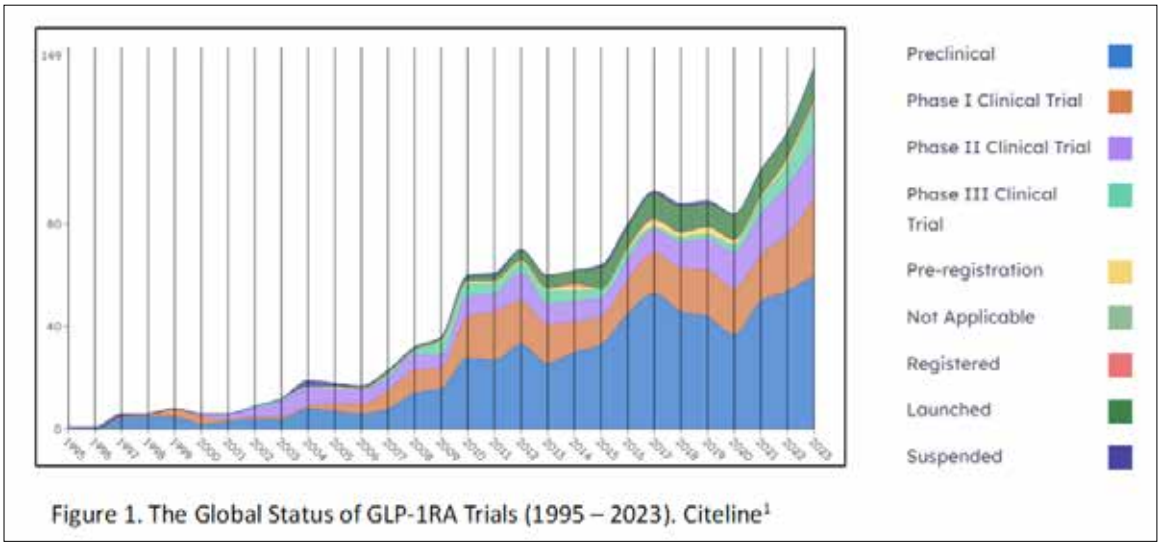

Figure 1. The Global Status of GLP-1RA Trials (1995 – 2023). Citeline[1]

Figure 1: The global status of GLP-1RA trials (1995-2023)[1]

dysfunction-associated liver disease (MASH), and a GLP-1RA or GLP-1/GIP RA + PYY analogue for obesity.

Small molecules

The increasing pipeline of nonpeptide GLP-1RAs offers the potential for oral therapy with differentiated effects across the spectrum of metabolic disease. While no orally available small molecule GLP-1 receptor agonist has yet been developed, some have entered clinical trials (eg, orforglipron, danulglipron and lotiglipron).

The growing global burden of childhood obesity has reinforced the need for oral therapies, which may help address the challenges with compliance in children and adolescents as well as those with a resistance to injectable therapy.

A common metabolic space

GLP-1RAs do not respect the traditional boundaries between medical specialties, demanding a broader focus for this common metabolic space.

Obesity

As noted, the effects of GLP-1s on obesity have been the single most important driver in the explosion of research into GLP-1RA-based therapies, in what has been described as a 'revolution in obesity treatment.'[3] Until recently, the development of pharmacological therapies for treating obesity has been beset by failure: 25 agents were withdrawn post-marketing between 1964 and 2009 (eg, rimonabant, sibutramine, phentermine, methamphetamine and dexfenfluramine) due to safety concerns.

Metabolic and bariatric surgery (MBS) is associated with 59% and 30% reductions in all-cause mortality among obese adults with or without type 2 diabetes, respectively, and most patients undergoing surgery show improvement, or complete resolution, of their underlying T2DM, dyslipidaemia, hypertension and sleep apnoea.[4] Despite the increasing safety and availability of MBS, it is only performed on less than 1% patients who fulfil the criteria for surgery and is unable to meet the growing needs of the worldwide obesity epidemic.One of the most significant hormonal changes to occur after MBS is the elevation of circulating GLP-1, and this observation has provided the template for the development of the new, more powerful GLP-1-based obesity therapies.

The SCALE study, which used 3mg liraglutide once daily compared to the standard doses of 1.2 and 1.8mg used in treating T2DM, showed that higher doses of GLP-1 therapies are required in treating obesity.[5] This observation was further confirmed in the STEP studies, which used semaglutide 2.4mg weekly (compared to the earlier doses of 0.5mg, 1.0mg and 2.0mg).

While the initial studies with liraglutide showed a modest effect on weight loss in obese subjects (6% weight loss over 52 weeks in participants with T2DM), the higher semaglutide dose (2.4mg weekly) reset the bar for obesity treatment (**Figure 2**).[6]

More recently in the SURMOUNT-1 trial, tirzepatide 5mg, 10mg and 15mg weekly showed a mean body weight loss of 15, 19 and 21%, respectively, compared to 3% in the placebo arm.[7] In November 2023, tirzepatide (Zepbound) joined two other GLP-1RA based obesity therapies (liragutide 3mg [Saxenda] and semaglutide 2.4mg [Wegovy]) approved by the US Food and Drug Administration (FDA), and received approval for treatment of obesity (BMI ≥30kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbidity (hypertension, T2DM or hypercholesterolaemia).

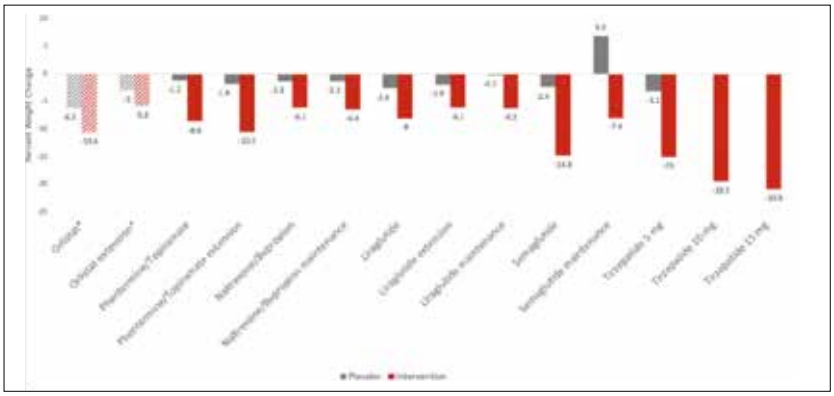

Figure 2: Mean percentage (%) weight changes in the main phase 3 trials of the FDA-approved anti-obesity medications showing the impressive comparative efficacy of semaglutide and tirzepatide

The results of the T2DM phase 2 retatrutide (GIPR/GLP-1R/GCGR tri-agonist) study, which were presented at the American Diabetes Association (ADA) 83rd Scientific Sessions in June 2023, may have raised the obesity treatment bar another notch, with dose-dependent body weight reductions of up to 16.94% (12mg escalation group) at 36 weeks that did not appear to have reached a plateau at the end of the study.[8] This is the highest weight loss reported so far on any GLP-1-based therapy.

CVD

Until the revised FDA Draft Guidance for Industry (2020), between 2008 and March 2020, all GLP-1 therapies for T2 diabetes were required to show CV safety (major adverse cardiovascular events [MACE] near or below 1.0; Cardiac Index ≤3), and the results of all these preregistration studies suggest a positive class effect of GLP-1RA therapies on CVD. It is noteworthy that albiglutide showed a reduction in MACE despite only modest weight loss, suggesting that the CV benefit is independent of the effect on obesity.[9]

Possibly the most exciting recent study on GLP-1RA therapies is the recently published SELECT Study.[10] This study enrolled a non-diabetic population (n=17, 604) with overweight or obesity and preexisting CVD who were randomised to receive semaglutide 2.4mg or placebo for more than three years. Compared to those on placebo, participants on semaglutide showed 20% lower risk of heart attack, stroke or death due to CVD and lost an average of 9.4% of their body weight. It remains to be seen how this study will impact clinical guidelines for CV risk reduction in non-diabetic obese or overweight persons at high CV risk and for further studies to clarify whether this is a class effect of GLP-1RAs.

CKD

GLP-1RAs have shown significant benefits in CKD (reduced new-onset macroalbuminuria, reduced uric acid excretion and slowed decline in estimated glomerular filtration rate [eGFR]), and are currently recommended by Kidney Disease Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guidelines as second-line therapy for glucose lowering in T2DM and CKD in patients not attaining their therapeutic goals despite sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Preferential use of GLP-1RAs is also recommended in patients with T2DM, obesity and CKD to promote weight loss.[11]

Metabolic dysfunction-associated steatotic liver disease (MASLD)

Considering that the key drivers for development of MASLD are insulin resistance and obesity, it is logical that GLP-1-based therapies have become therapeutic targets for MASLD. Both liraglutide and semaglutide have shown therapeutic benefit on steatosis, liver inflammation and potentially degree of fibrosis in patients with MASH. The liver does not, however, have receptors for GLP-1 (or GIP), and the effects of GLP-1 agonism are indirect and probably related to drug-induced weight loss.[2]

The liver does have glucagon receptors (GCGRs), and due to the differential metabolic effects of glucagon on the liver, GCGRs containing co-agonists and tri-agonists have become attractive targets for treatment of MASLD. There are currently at least five GLP-1/GCGR co-agonists in phase 2 or 3 development. Cotadutide, a GLP-1/GCGR co-agonist, showed reduced body weight, improved glycsemia and reduced hepatic steatosis, but development has been terminated.

Along with the impressive weight loss, the MASLD subgroup of the phase 2 obesity trial of retatrutide 12mg showed 81.4% greater reduction in liver fat than placebo, and 100% of participants achieved ≥30% reduction in liver fat by 24 weeks.[12]

Clinical research challenges and future directions

While the extensive data on GLP-1 therapies have shown favourable risk-benefit, the combination of gastrointestinal side effects (mainly nausea, vomiting and constipation), non-responders to active therapy, and limitations on placebo therapy present a clinical and research challenge.

The dropout rates in studies that include GCGR co-agonists (survodutide 4.8mg) have also been noted to be high (24.7%) compared to semaglutide 2.4mg in the STEP 1 trial (3.9%) and tirzepatide in the SURMOUNT-1 trial (3.6%). However, this trend was not noted in the phase 2 retatrutide trial, where only six out of the 190 (3%) participants withdrew due to gastrointestinal adverse events. Protocol design and site-level mitigations are key to mitigating the risk of dropouts. In addition, a low starting dose and long titration interval are critical to achieving target level exposure to a study drug. J.P. Morgan Chase & Co. has predicted that total GLP-1

users in the US may number 30 million (9% of the overall population) by 2030.[13] Placebo-controlled trials will become increasingly difficult to justify in the face of this shrinking pool of GLP-1 naïve patients and the increasing availability of effective therapies. Preplanned strategies for meaningful lifestyle and nutritional support are required to maintain participant engagement throughout a study. Open label extensions using active therapy also provide a useful incentive to maintain retention during the blinded phase of a trial. The under-representation of Black and other ethnic and racial minorities in GLP-1 trials has reduced the statistical power of GLP-1RA efficacy in some populations due to small sample sizes. The evidence suggesting that beneficial effects may not be consistent across all populations reinforces the need to include diverse populations in GLP-1RA based clinical trials.[14]

Many of the unanswered questions related to long-term GLP-1 therapy, such as optimal weight maintenance strategies, body composition changes and long-term safety, will be best addressed using real-world data. The recent Presidential Advisory from the American Heart Association is a timely reminder that clinical research into GLP-1 therapies is predicated on a unified approach across a broad range of medical specialties including endocrinologists, diabetologists, internists, cardiologists, nephrologists, neurologists and family practitioners.[15]

The GLP-1 space is evolving rapidly and becoming increasingly crowded, but the different beneficial effects on the multiple outcomes of cardiovascular-kidney-metabolic syndrome and increasing specificity of actions will open the door to precision medicine.

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