# Once-Weekly GLP-1 Receptor Agonists: Moving The Goal Posts

Abd A Tahrani[1,2,3], Srikanth Bellary[3,4], Anthony H. Barnett[1,3]

[1]Institute of Metabolism and Systems Research(IMSR), University of Birmingham, Birmingham, UK

[2]Centre of Endocrinology Diabetes And Metabolism (CEDAM), Birmingham Health Partners, Birmingham, UK

[3]Department of Diabetes and Endocrinology, Heart of England NHS Foundation Trust, Birmingham, UK

[4]School of Life & Health Sciences, Aston University, Birmingham, UK

Corresponding author:

Abd A Tahrani

Institute of Translational Medicine,

University Hospital of Birmingham

Birmingham B15 2TH

UK

a.a.tahrani@bham.ac.uk

Glucagon like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs) for the treatment of Type 2 Diabetes (T2DM) were first introduced to Europe and the USA in 2005(1) . Since then, they have become well-established treatment options in the management of T2DM(2). GLP-1 RAs have several attractive features including: potent and sustained glucose lowering, low risk of hypoglycaemia due to their glucose-dependent effects on insulin and glucagon secretion, sustained weight-loss, and a favourable impact on cardiovascular risk factors together with reduction in cardiovascular event rates (liraglutide and semaglutide)(1;3-5). Several injectable GLP-1 RAs are now licensed for the treatment of T2DM, and other approaches including oral and continuous delivery via an osmotic mini-pump are in development(1;6;7), offering patients a range of dosing and delivery regimens. Together, the clinical attributes and delivery options may be very attractive to patients and health care professionals (HCPs) with the potential to reduce clinical inertia, improve therapy adherence and achieve sustained glycaemic control(8). On the other hand, the intra-class differences in the pharmacokinetic and pharmacodynamic properties of these agents raises challenges in terms of individualising treatment. Hence, there is a need for head-to-head trials comparing the efficacy, safety and acceptability of GLP-1 RAs(9).

In this issue of the Journal, Pratley et al present their findings from SUSTAIN 7, a multi-centre, randomised, open-label, phase 3b trial of two once weekly GLP-1 RAs, semaglutide vs. dulaglutide, in patients with T2DM inadequately controlled with metformin (**REF TO BE INSERTED**). Over 40 weeks, whilst both agents showed good glycaemic efficacy, semaglutide was superior to dulaglutide in terms of the HbA1c -lowering and weight loss despite the higher use of rescue treatment in the latter group. In addition, more patients randomised to semaglutide achieved the composite secondary outcome of HbA1c <7·0% (53 mmol/mol) without severe or confirmed symptomatic hypoglycaemia and no weight gain compared with dulaglutide.

Superior clinical efficacy, however, should always be considered in the context of safety. The adverse events profiles were largely comparable between the two agents and consistent with expectations from the class. Premature treatment discontinuation, however, occurred more frequently with semaglutide, mostly due to gastrointestinal side effects. Nonetheless, treatment discontinuation was uncommon affecting < 10% of patients. Diabetic retinopathy (DR) is another important safety concern in the light of results from SUSTAIN 6(5). The current study shows no evidence for increased risk of progression of DR with semaglutide, but the SUSTAIN 6 population were at higher cardiovascular risk and patients with proliferative DR or maculopathy were excluded from SUSTAIN 7. There is still a need, therefore, for further data regarding the effects of semaglutide on DR.

Differences in efficacy between GLP-1 RAs have been observed in several head-to-head trials(9) without clear explanations. Efficacy differences in the current trial could be due, at least in part, to differences in the structure and size of semaglutide (a GLP-1 analogue with a fatty diacid chain) and dulaglutide (two copies of a GLP-1 analogue with amino acid substitutions Ala8Gly, Gly22Glu and Arg36Gly, covalently linked to an Fc fragment of human IgG4) molecules(1). This might result in a differential ability of the GLP-1 RA to reach the appetite control centres in the brain and hence provoke differences in weight loss, leading to differences in the glucose lowering efficacy of these two molecules. However, this hypothesis needs to be tested and the current study does not explore whether the greater weight loss with semaglutide is responsible for the greater HbA1c reductions in the semaglutide arm.

Mode and ease of drug delivery (particularly in the context of injectables) are important factors in the context of treatment acceptability and adherence. The present trial delivered both study drugs using their respective licensed devices. Comparing patient views on usability and acceptability of the injection devices, however, was not part of the study design, although measures of treatment satisfaction and quality of life showed no differences between semaglutide and dulaglutide. Future

studies should examine patient preferences in terms of the devices used as this might have implications in real life.

When choosing the "next" glucose lowering agent in patients with T2DM, HCPs need to consider multiple factors in addition to glycaemic efficacy in order to personalise treatment approaches based on individualised treatment targets. Such factors may include the impact on weight, hypoglycaemia, cardiovascular risk, diabetes-related complications, tolerability, ease of use, durability of effects, interactions with other agents, patients age and renal and/or hepatic impairment. Whilst 2 head to head trials of semaglutide versus other weekly GLP-1 RAs (the current trial and SUSTAIN 3)(10) demonstrate glycaemia and weight advantages of semaglutide, treatment decisions should allow for differences in trial designs and the generalisability of the findings in a real life setting. For example, the SUSTAIN 7 findings apply to patients who were only on metformin and who were at relatively low cardiovascular risk since patients with renal impairment, established cardiovascular disease and advanced DR were excluded. In addition, much more information as to the relative utility within class of these agents from Real World settings is required to establish their true place in the management of T2DM.

## Reference List


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