Once-weekly glucagon-like peptide 1 receptor agonists
Sanjay Kalra,1 Yashdeep Gupta2

Abstract
The once-weekly glucagon-like peptide 1 receptor agonists (QW GLP1RA) represent a major advancement in diabetes pharmaco-therapeutics. This review describes the basic, clinical, and comparative pharmacology of this novel class of drugs. It highlights the clinical placement and posology of these drugs.

Keywords: Albiglutide, dulaglutide, exenatide QW, semaglutide.

Once-Weekly Diabetes Therapy
Diabetes is a chronic condition which needs long term therapy. This therapy is often complex and intrusive, and may not be welcomed by people with diabetes. A new class of drugs, currently under development, allows the freedom and flexibility of once-weekly injections. The class of long-acting GLP1RA (glucagon-like peptide-1 receptor agonists), which includes exenatide LAR (long acting release), dulaglutide, albiglutide and semaglutide, consists of molecules with a protracted duration of action, that allow once-weekly dosage (Table). This review describes currently approved options for once-weekly therapy of diabetes, while mentioning drugs in development as well.

Mechanism of Protraction of Action
Exenatide QW is a modified version of exenatide, which is encapsulated in microspheres to ensure protraction of action. The formation uses microsphere drug delivery technology to prolong the duration of action of exenatide, and reduce its peak-trough ratios. Patented Medisorb microspheres, composed of a bio-degradable polymer that breaks down into carbon dioxide and water,
allow slow release of the drug.\textsuperscript{1}

Dulaglutide consists of two GLP-1 analogues (made relative resistant to degradation by DPP-4, by substitution of alanine by glycine at position 8), each covalently linked to the Fc portion of human IgG4 antibody. This structure creates a large sized molecule which reduces renal clearance and increases time-action profile. An optimized amino acid linker is inserted to improve binding and prolong the half life of dulaglutide. Solubility is ensured so as to allow injection through a 29 G thin needle. Immunogenicity is minimized by various structural modifications.\textsuperscript{2}

Albiglutide is a large-sized molecule created by fusing a GLP-1 dimer to recombinant albumin, such that the rate of renal filtration is slowed down.\textsuperscript{3}

\textbf{Kinetics}

Exenatide QW reaches therapeutic concentration after 2 weeks, and attains steady-state at 6-7 weeks.\textsuperscript{4} Dulaglutide has a half life of 4.7 days, and attains steady state within 2-3 weeks.\textsuperscript{5} Albiglutide has a half life of 5-8 days, and displays a pharmacokinetic profile similar to that of other once weekly GLP1RAs.\textsuperscript{6}

\textbf{Dynamics}

Exenatide QW achieves mean HbA1c reductions of -1.3 to -1.9%, which are significantly greater than that of sitagliptin and exenatide twice daily. Weight loss varies from -2.7 to -3.7kg, and is significant greater than weight changes noted with glargine. In a three year long open-label extension, exenatide QW was able to achieve and maintain, a significantly lower HbA1c than glargine, while causing significantly less hypoglycaemic episodes.\textsuperscript{7}

Dulaglutide (1.5mg/week) has been found to be superior to placebo, exenatide twice daily, insulin glargine, metformin and sitagliptin. The same dose has been found to be non-inferior to liraglutide 1.8mg, An HbA1c reduction of 0.8-1.6% is accompanied by a weight loss of up to 3.2kg. The unique feature of dulaglutide is that it is able to achieve better post prandial glycaemic control than the short-acting exenatide, while providing adequate fasting control as well.\textsuperscript{5}

Albiglutide has been found to achieve adequate glycaemic control, though this is significantly less as compared to pioglitazone and liraglutide. A weight loss of up to 1.1kg has been reported.\textsuperscript{6}

\textbf{Adverse Effects}

All once weekly GLP1RAs are associated with transient gastrointestinal effects such as nausea and vomiting, and should be used with caution in gastroparesis. Exenatide QW administration may lead to injection site cutaneous nodules.\textsuperscript{7} Antibodies may develop in patients exposed to these drugs; however, this is not of clinical significance.

\textbf{Posology}

Exenatide QW is available as a 2 mg dose, to be reconstituted prior to administration by a syringe and needle. Dulaglutide is available in two strengths: 0.75mg and 1.5 mg, as prefilled disposable pens. The lower dose is recommended in elderly persons and those with moderate renal failure. Albiglutide is approved as 30 mg or 50mg weekly doses, which need to be reconstituted prior to use. Initiation should be with the lower dose, which can be up-titrated if necessary.

\textbf{Clinical Usage}

These drugs are approved for use as adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes. Though studied as monotherapy, they are not currently advised as alternatives to metformin. They can be used, however, in persons who do not respond to metformin monotherapy and need intensification of therapy.

All drugs can be administered once weekly at any time of the day, without reference to meal times, in the subcutaneous tissue, using product-specific single use pens. Exenatide QW and albiglutide need to be reconstituted immediately prior to use, but dulaglutide is available as a prefilled, single use, disposable pen. While exenatide QW is injected through a 23G needle, albiglutide and dulaglutide use 29G needles for drug delivery.

These drugs have the potential to be used as Directly Observed Therapy (DOT) in persons who are unable to, or unwilling to, self-inject, and prefer injection administration by health care professionals or other persons.\textsuperscript{8}

\textbf{Semaglutide}

Semaglutide is a structural analogue of liraglutide which has greater albumin binding and increased resistance to cleavage by DPP4. Doses of 0.5 and 1.0 mg/week are being evaluated in the SUSTAIN phase 3 programme.\textsuperscript{9}

\textbf{Summary}

The QW GLP1RA are a novel class of anti-diabetic drugs which hold potential for use in clinical practice. The drugs exenatide QW, dulaglutide and albiglutide can be used once weekly, in combination with other glucose-lowering drugs, to provide safe, well tolerated glucose control.
References