GLP-1 receptor agonists: why is once weekly inferior to once daily?

In *The Lancet Diabetes & Endocrinology*, Richard Pratley and colleagues report the results of a phase 3 registration trial of albiglutide, a new once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist.[1] Albiglutide is a unique chemical entity with a high molecular weight, composed of two GLP-1 molecules fused to an albumin molecule, and has a half-life of 5 days.[2] In their noninferiority trial, Pratley and colleagues found that albiglutide caused fewer gastrointestinal adverse events than the once-daily comparator, liraglutide (such events occurred in 36% of patients given albiglutide *vs* 49% of those given liraglutide). However, albiglutide had lower glycaemic efficacy than liraglutide: change in HbA_{1c} from baseline to week 32 was –0·78% for albiglutide versus –0·99% for liraglutide (treatment difference 0·21%, 95% CI 0·08–0·34; p value for non-inferiority=0·0846). Similar findings were also noted in a previous trial that compared exenatide—the only other once-weekly GLP-1 receptor agonist developed so far—with liraglutide.[3]

Similar to the pharmaceutical evolution of bisphosphonates, which has been characterised by the development of drugs with ever-longer half-lives and thus wider intervals between doses, GLP-1 receptor agonists have been developed with increasingly longer half-lives to minimise the frequency of injections—a factor that is viewed as a substantial barrier to acceptance and adherence with injectable drugs in patients with type 2 diabetes. In 2005, the first clinically useful GLP-1 receptor agonist, exenatide, was approved by the US Food and Drug Administration. This drug has a short half-life of 2 h and is injected at least twice daily.[4] For reasons intrinsic to the molecule, a high rate of gastrointestinal adverse events occurs with this drug and therefore progressive titration is necessary to minimise these effects. To further limit the number of injections and also to reduce the gastrointestinal adverse effects of this short-acting form of exenatide, a long-acting weekly version has been developed (Bydureon [Amylin Pharmaceuticals Division of Bristol-Myers Squibb, Princeton, NJ, USA]). This weekly version shows better glycaemic control and better tolerability than the twice-daily version,[5] which has guided the development of other long-acting GLP-1 receptor agonists. This focus on lengthening of the half-life of GLP-1 receptor agonists follows a similar developmental pathway to that of insulin, for which increasingly long-acting preparations were developed in the 1930s and 1940s to minimise injection frequency. Although this approach was advantageous for insulin in the early 20th century because of the onerous nature of injection equipment before the availability of disposable needles and syringes, injection technology has improved greatly since that period. Now, extremely small gauge needles and improved pen devices are routinely used to make the injection experience much more patient friendly than it was in the past. Any remaining reluctance to initiate insulin therapy now seems to reside in patients' perceptions of insulin.[6]

Unlike insulin, patient acceptance of GLP-1 receptor agonists is quite high, which could be attributable to the extremely low risk of hypoglycaemia with GLP-1 receptor agonists versus insulin, or the potential for weight loss with GLP-1 receptor agonists versus the usual weight gain reported with insulin, or both. Similar to insulin, administration of GLP-1 receptor agonists is aided by the availability of small-diameter disposable needles and syringes, and by the use of disposable pens. Unlike bisphosphonates, few restrictions exist on activity or ingestion of food and liquid immediately after administration of a GLP-1 receptor agonist. Thus, the problematic administration issues of bisphosphonates do not exist with the GLP-1 receptor agonists. The implied premise that underlies the use of weekly GLP-1 receptor agonists is that they will help patient persistence and adherence to this medication. However, this concept is unproven in the present study with albiglutide and also remains unproven with weekly exenatide.

In comparison studies of liraglutide versus weekly GLP-1 receptor agonists exenatide and, now, albiglutide, the long-acting GLP-1 receptor agonists were inferior in terms of improvements in glycaemic control.[1,3] No a-priori basis exists by which to account for the consistent finding that the long-acting drugs are inferior in terms of lowering HbA_{1c}. Indeed, this finding is counterintuitive since the long-acting drugs should



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maintain greater degrees of receptor saturation for far longer periods of time than does the once-daily drug. This result likely derives from systematic errors in dose estimations with the weekly drugs, from deliberate selection of suboptimum doses with respect to glycaemic control in favour of lower toxicity, or from fundamental differences in these agents' interactions with the GLP-1 receptor compared with liraglutide. The weekly form of exenatide has notable skin reactivity, and the twice-daily form is associated with substantially more gastrointestinal adverse events, compared with liraglutide. However, the weekly form had fewer gastrointestinal adverse events than did liraglutide,[5] which might be representative of the elimination of peaks and valleys from the kinetics of twice-daily exenatide compared with the comparatively smooth kinetics of the weekly form of the drug.

Future studies might show that dose titration of long-acting GLP-1 receptor agonists can allow glycaemic control comparable to that of daily forms, and determine whether there are differences in how molecules in this drug class interact with the GLP-1 receptor. Meanwhile, Pratley and colleagues have provided evidence that albiglutide is a safe, effective, and well-tolerated weekly GLP-1 receptor agonist, which should advance the ability to control hyperglycaemia in many patients with type 2 diabetes.

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