COMMENTS AND RESPONSES

Comment on: Butler et al. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: Are the GLP-1 Therapies Safe? Diabetes Care 2013;36:2118–2125

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In the July issue, Butler et al. (1) published a "point" narrative of a two-part Point-Counterpoint addressing the safety of glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors. The review contains factual errors and some nontransparent or not fully elucidated statements relating to previously published studies.

Nyborg et al. (2) reported the nonclinical pancreas toxicology data of liraglutide in ~1,200 animals. Butler et al. refer to these data as treatment being stopped 2 weeks before the evaluation of tissues in nonhuman primates. This is incorrect. All the data reported in Nyborg et al. are from animals killed while on liraglutide treatment. Age was recorded for all animals, and treatment continued for 2 years in rodents and 87 weeks in nonhuman primates.

Vrang et al. (3) reported data from diabetic ZDF rats, and again found no pathology induced by liraglutide, including proliferation. Butler et al. suggest that the proliferation data could be unreliable because the histological tissue sections had been formalin-fixed. Endocrine as well as exocrine cell replication was clearly measurable. High proliferation rates were found in all animals, highest in the different control groups. Vrang et al. applied stereology for evaluating the changes. Stereology is the only method that eliminates sampling bias and takes the three-dimensional structure of the organ into consideration (4). Butler et al. also bring into question the cause of death of three rats on liraglutide. However, this information is well described in the article. The control animals erroneously had a very high dose of liraglutide. All animals in the dedicated liraglutide groups survived the entire treatment period.

Butler et al. mention that human duct cells and pancreatic intraepithelial neoplasia lesions contain GLP-1 receptors. These conclusions are based on studies using polyclonal antibodies to detect GLP-1 receptors. Antibodies against G-protein–coupled receptors are notoriously known for being unspecific, and new guidelines are being introduced by journals requiring authors to document specificity of antibodies (5). Receptor expression measured by ligand binding is not subject to such error; using such techniques, pancreatic adenocarcinomas did not express GLP-1 receptors (6).

We find it important that studies aiming to describe potential side effects of therapies for human use are carefully designed, have clear hypotheses, and use proper methodology. Antibody-independent methods (e.g., in situ ligand binding) should be used to secure reliable documentation of receptor expression. Studies examining changes in cell mass or cell proliferation should apply principles of stereological sampling.

Based on the totality of information available to Novo Nordisk, there is no clear evidence that liraglutide increases the risk of pancreatitis or pancreas cancer in humans. The ongoing Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study (clinical trial NCT01179048) will prospectively evaluate the overall safety of liraglutide. The trial has enrolled 9,340 patients with type 2 diabetes. Adjudication of all adverse reactions related to pancreatitis and any neoplasm is an integral part of the protocol. Randomized, controlled, long-duration trials with independent adjudication are the only way to evaluate rare side effects, as also mentioned by Kahn recently (7). The LEADER study will report in 2016.

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