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EDITORIAL

Hepato-preferential insulins: Is this the end, or the end of the beginning?

Basal insulin peglispro (BIL) is a novel insulin analogue that binds insulin lispro covalently via a urethane bond to a 20-kDa polyethylene glycol molecule (PEG). This analogue, therefore, has a molecular weight of ~25.8 kDa, approximately three times greater than that of native insulin or most insulin analogues. Its hydrodynamic size, however, appears to be even larger, ~90 kDa, similar to a globular protein such as human albumin.[1] BIL has less insulin receptor-binding affinity in comparison to insulin, but at the cellular level, the mechanism of insulin receptor engagement and activation for BIL is similar to that of human insulin.[2] The insulin moiety of BIL is degraded in a similar way to human insulin. The PEG backbone is recycled out of the cell[3] and excreted from the body via both renal and hepato-biliary routes. The pharmacokinetic profile of pegylated lispro is prolonged when administered by subcutaneous injection, with a half-life of 2-3 days, which is significantly longer than that of any of the other available insulin analogues.[1] It has been proposed that large insulin analogues must pass through the capillary wall, lined by a continuous endothelium, and the rate of diffusion is inversely related to their molecular size.[4] In contrast, within the liver there are highly fenestrated cells that line the vascular sinusoids and thus there is no barrier to prevent insulin diffusion.[4] In normal physiology, insulin is secreted by the pancreas into the hepatic portal vein that delivers insulin directly to the liver and thus the liver sees four times the concentration in comparison with other tissues supplied by the systemic peripheral circulation.[4] It has therefore been proposed that larger insulin molecules are more likely to be relatively hepato-preferential, and some have suggested this might be a strategy to achieve more physiological insulin replacement via the subcutaneous route.

Moore et al.[5] in animals and Henry et al.[6] in humans have shown that BIL has preferential hepatic versus peripheral action compared with conventional insulin. The detailed protocol of the human studies is reported in the present issue and accompanying supplement within an elegant comparative clamp protocol.

BIL subsequently underwent small-scale phase II studies which had promising results, with greater glycated haemoglobin (HbA1c)-lowering, weight reduction and fewer nocturnal hypoglycamic episodes than comparator insulin analogues.

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An extensive phase III clinical trial programme (IMAGINE) has just been completed, with large numbers of participants. A total of six comparator clinical trials (five with insulin glargine and one with NPH insulin) and an additional trial comparing flexible timing of BIL administration have been performed, and the results are presented in this issue of *Diabetes Obesity and Metabolism*, accompanied by a supplement. All seven trials used treat-to-target designs. A total of 3859 patients received BIL [type 1 diabetes (T1DM), n = 1238; type 2 diabetes (T2DM), n = 2621] for 3051 patient-years, with exposure for up to 18 months, and a total of 2352 patients (T1DM, n = 676; T2DM, n = 1676) received an active comparator for 1821 patient-years. The IMAGINE programme is notable as the first to use double-blind administration of different types of insulin. As a result of this, the results are particularly robust and consistent. All these trials are published in the present issue of and supplement to *Diabetes Obesity and Metabolism*, and demonstrate clinical utility both in patients with T1DM and in those with T2DM. BIL was found to be superior to comparator glargine in all studies, with a statistically significantly greater reduction in HbA1c. There were fewer nocturnal hypoglycaemic episodes and reduced weight gain, or in some T1DM studies, weight loss. Although the results were encouraging, there were some significant problems. Injection site reactions and elevation of liver enzymes were noted in some patients. In addition, triglycerides were also mildly elevated with BIL compared with glargine. There was also, particularly in the patients with T2DM already on basal insulin, an observed modest increase in liver fat compared with glargine. By contrast, there was no increase in liver fat in insulin-naive patients randomized to BIL, but a reduction in those randomized to glargine. This observed difference may shed light on aetiology, and this is explored in more detail in one of the papers within the supplement.

The big question that has very significant implications for the development of insulin replacement therapies involving hepato-preferential insulin analogues is as follows: are the adverse liver and lipid changes a physiological response to giving a more hepato-preferential insulin or are the effects toxic, secondary presumably to the novel structure and nature of this insulin? The clinical trial programme has recently been terminated as it was felt that studies to determine the mechanism for the changes in both liver function, accumulation of liver fat and the small rise in triglycerides were unlikely to reassure regulatory authorities. What is not clear, but of

wider interest, is whether these changes resulted from the physiological hepato-preferential action of this analogue or whether they are specific to BIL. The papers in the present issue of the journal and accompanying supplement detail the clinical utility of BIL both in patients with T1DM and in those with T2DM, and also discuss in detail the hepato-preferential mechanisms and provide an insight into the liver effects of this unique insulin. Other hepato-preferential insulin analogues are under development, and the present papers provide a considerable resource and insight into the potential advantages and disadvantages of this class of insulin analogue.

I hope this is only the end of the beginning and that others will not be deterred in the future from developing hepato-preferential analogues that offer such potential advantages.

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