INVESTIGATING THE DIFFERENT DIMENSIONS OF DPP-4 INHIBITORS

Summary of Presentations from the Takeda Pharmaceuticals International-Sponsored Symposium, held at the 50th Annual Meeting of the EASD, Vienna, Austria, on 15th September 2014

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MEETING SUMMARY

This Takeda-sponsored European Association for the Study of Diabetes (EASD) symposium addressed the pharmacology, clinical use, and future therapeutic application of dipeptidyl-peptidase-4 (DPP-4) inhibitors. The scientific programme covered the clinical efficacy of DPP-4 inhibitors, their durability in clinical practice, and their use in combination therapy with other antidiabetic drugs. The important issue of the effect of this class of drugs on cardiovascular (CV) outcomes was also explored. The symposium was chaired by Prof Heinz Drexel and included insightful talks from an expert faculty comprising of Profs Jørgen Rungby, Jochen Seufert, and Kausik Ray.

Welcome to Different Dimensions of DPP-4 Inhibitors

Professor Heinz Drexel

Prof Heinz Drexel introduced the session by outlining the agenda of the symposium and introducing the faculty members and main themes. These included the pathophysiology and epidemiology of diabetes, and the exploration of pharmacology of DPP-4 inhibitors and their durability and application in clinical practice. This was followed by a discussion of the data linking

insulin resistance and CV disease, which formed the basis for an introduction to recent data from CV outcomes trials for the currently available DPP-4 inhibitors.

The Structural Dimension: Exploring the Pharmacology of DPP-4 Inhibitors in More Detail

Professor Jørgen Rungby

Impaired regulation of insulin is a known contributor to hyperglycaemia[1] and the pathophysiology of Type 2 diabetes (T2D). Defects in the secretion and action of the two main incretin hormones, gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), contribute to this. GIP facilitates fat deposition, promotes bone formation, increases glucagon production, and decreases gastric acid secretion;[2] while GLP-1 is involved in gastric emptying, increasing insulin production, and decreasing glucagon production. It also plays a role in increasing cardiac output and has a cardioprotective effect, particularly during ischaemia.[2] Both GIP and GLP-1 are involved in increasing beta cell mass and insulin production.[2] These incretin hormones work in conjunction to lower glucose levels and therefore prevent hyperglycaemia, one of the hallmarks of T2D.

Following ingestion of a meal, levels of GLP-1 increase in the portal vein and in the peripheral circulation, increasing meal-stimulated insulin secretion, and thereby reducing liver glucose production and increasing peripheral glucose uptake.[3,4] Endogenous GLP-1 stimulates insulin secretion directly but also via afferent neurones located in the intestines, portal vein, and/or liver.[5] The ability of incretin hormones to stimulate insulin secretion after meals has been dubbed 'the incretin effect'. The impaired incretin response observed in T2D has been associated with decreased levels of GLP-1.[6] GLP-1 and GIP have a half-life of 2 and 5–7 minutes, respectively, due to their rapid inactivation by DPP-4 and clearance via the kidneys.[7,8] Therefore, inhibition of DPP-4 results in increased plasma levels of GLP-1 following meal stimulation, a reduction in glucagon secretion, an increase in insulin release, and subsequent lowering of blood glucose levels.[9] DPP-4 inhibitors have several clinical benefits, including their ability to reduce glycated haemoglobin (HbA1c) by, on average, 0.5–0.8%, a reduction which is enhanced when they are used in conjunction with insulin, thiazolidinediones (TZDs), metformin, or sulphonylureas (SUs).[10] Generally, DPP-4 inhibitors are well tolerated as mono and combination therapies, even in patients with renal insufficiency. They are associated with only a minimal risk of hypoglycaemia and weight-neutral effects, characteristics that may increase patient adherence to this therapy.[10]

Alogliptin is the most recent addition to the DPP-4 inhibitor class, which has been shown to be selective for DPP-4 over other DPP enzymes, including DPP-8 and DPP-9, and to have a long half-life and favourable safety profile. These properties, in addition to the pathways utilised for their metabolism and excretion, and their suitability for use in special populations, their glycaemic efficacy, and potential for interactions with other drugs, should be considered when choosing between the currently available DPP-4 inhibitors.[11]

One important factor that differentiates the individual DDP-4 inhibitors is the number of sites they are able to bind to on the DPP-4 enzyme. The higher the number of points of interaction, and the closer these are to the active site of the enzyme, the higher the selectivity and efficacy of the inhibitor.[12,13] Due to the distribution of DPP enzymes throughout the body, selective inhibition is extremely important; the DPP-4 inhibitors alogliptin and linagliptin have been shown to be highly selective for DPP-4 over DPP-8 and 9 *in vitro*, in comparison with saxagliptin, sitagliptin, and vildagliptin.[12] In addition, DPP-4 inhibitors, including alogliptin, have been shown to be suitable for use in special populations, including in the elderly and in individuals with mild-to-moderate hepatic and renal insufficiency.[14,15] Key differentiating characteristics of DPP-4 inhibitors include their chemical structure, metabolism, *in vitro* selectivity, dosing frequency, and their use in special patient populations.

The Clinical Dimension: Efficacy and Durability of DPP-4 Inhibitors in Practice

Professor Jochen Seufert

The incidence and prevalence of T2D is increasing across the world, with the biggest increase in prevalence observed in the Far East, the Western Pacific, Africa, and South America.[16] T2D is a

progressive disease associated with a decline in endogenous insulin secretion, and with progression, eventual treatment intensification in order to maintain control of blood glucose levels in patients is required. Due to the need for treatment intensification, antidiabetic drugs must also allow for the possibility of broad combination therapy and have a favourable CV safety profile.[17] Over the past 20 years the rate of introducing new classes of antidiabetic agents has increased, with DPP-4 inhibitors being amongst the newest and most effective class of drug now available.[18]

Despite the availability of newer agents, up to two-thirds of patients fail to achieve glycaemic targets.[19-21] As a consequence, treatment guidelines have been devised with the aim of optimising glucose control strategies. The American Diabetes Association/EASD guidelines recommend the use of biguanides (metformin) as a first-line therapy - a recommendation that is consistent with many other available guidelines.[22] However, recommendations for subsequent therapy intensification after first-line therapy differ between the various guidelines and include treatment with TZDs, GLP-1 receptor agonists, Sus, and insulin.[22] The decision to make the transition from first-line therapy to a more intensive treatment regimen is an issue frequently faced by physicians in the clinic. The action profile of anti-hyperglycaemic drugs should be favourable in terms of HbA1c reduction, blood pressure, and body weight, and be associated with a low risk of hypoglycaemia.[22] When compared against these criteria, DPP-4 inhibitors reduce HbA1c by up to 1.1%, with little effect on systolic blood pressure, neutral effects on body weight, and a low risk of hypoglycaemia.[22-24] The most common treatment strategy followed in 2014 was the addition of an oral agent to metformin, such as an SU, a DPP-4 inhibitor, or pioglitazone.[22] However, injectable therapies, including insulin, a GLP-1 agonist, or a combination of both, are alternative treatment strategies. More importantly, in order to achieve optimum glycaemic targets, the treatment regimen must be tailored to the patient and their individual treatment needs.[22]

A retrospective cohort study from the UK General Practice Research Database has shown that SUs remain the most popular second-line therapy.[25] This is despite evidence that patients initiating SU or metformin have an increased long-term risk of mortality and CV events compared to patients on metformin alone,[26] and that the durability of SU treatment for glycaemic control is reduced over time.[27] In contrast, DPP-4 inhibitors have demonstrated superior durable glycaemic control. A study comparing alogliptin and glipizide over 2 years has shown that alogliptin (12.5 and 25 mg) produced rapid HbA1c and fasting plasma glucose (FPG) reductions that were sustained over 104 weeks, and that were statistically superior to glipizide treatment for alogliptin 25 mg.[28] Additionally, there were significantly greater reductions in postprandial glucose with both doses of alogliptin versus glipizide, and a significant reduction in body weight and lower risk of hypoglycaemia with alogliptin treatment.[28]

The characteristics of DPP-4 inhibitors include their consistent HbA1c lowering effect, their long-term durability in maintaining glycaemic control, and their association with a low risk of hypoglycaemia. As a class they are well-tolerated, offer the possibility of broad combination therapy, and may have a favourable CV safety record.[17]

A New Dimension: What about Insulin Resistance? Exploring the Pioglitazone and Alogliptin Combination

Professor Heinz Drexel

Insulin resistance is caused by an interplay between genetic factors: abnormal insulin receptor function, abnormal signalling proteins, or abnormal insulin levels; and environmental factors such as obesity, a sedentary lifestyle, and ageing. It is often a combination of these that contribute to the characteristic hyperglycaemia, increased free fatty acids, and atherogenic lipid profile seen in individuals with T2D (Figure 1).[29] Patients with these clinical characteristics, who also display elevated FPG levels, a high body mass index, and increased urinary albumin excretion, are likely to have metabolic syndrome (MetS).[30,31]

The San Antonio Heart Study has demonstrated that as insulin resistance increases there is a proportional increase in the risk of cardiovascular disease (CVD).[32] Similar results have been found in a cohort of 750 patients undergoing coronary angiography, where a lower rate of glycaemic control was associated with a decrease in high-density lipoprotein cholesterol (HDL-C) and high levels of low-density lipoprotein cholesterol (LDL-C).[33] Over half of patients referred to a cardiologist displayed insulin resistance, indicating a link between insulin

resistance and increased risk of vascular events.[34] Therefore, pharmacological treatments that target insulin resistance may offer therapeutic benefit in the prevention of CV event risk. The UK Prospective Diabetes Study (UKPDS) has demonstrated that the rate of myocardial infarction (MI) was significantly lower in patients treated with metformin, than those treated with conventional therapy. These patients also had a lower rate of microvascular (MV) disease and a lower rate of death from any cause.[35]

Pioglitazone - an insulin sensitiser - decreases insulin resistance, enhances insulin action, and reduces blood glucose levels. In addition, it regulates the transcription of genes involved in carbohydrate, lipid, and protein metabolism;[36] these are favourable characteristics in treating patients with MetS. Pioglitazone monotherapy has been shown to provide durable glycaemic control and increase HDL-C, whilst lowering LDL-C levels, over 2 years in comparison to gliclazide, in patients with T2D.[37,38-40] In addition, macrovascular benefits on pioglitazone monotherapy have been demonstrated in several clinical trials. Monotherapy has been shown to reduce the risk of secondary stroke by 47% in patients with T2D[41] and in high-risk patients with T2D and previous MI; pioglitazone reduced the risk of secondary MI by 28%, and acute coronary syndrome by 37%.[42] Furthermore, in patients with chronic kidney disease, pioglitazone reduced the composite endpoint of all-cause death, MI, and stroke, independent of the severity of renal impairment.[43] However, pioglitazone is also associated with several risks, including increases in body weight due to fluid retention in the weeks following initiation of therapy.[44] Furthermore, a meta-analysis comparing both pioglitazone and another insulin sensitiser, rosiglitazone, with placebo or active comparator found an increased risk of bone fracture (p=0.001).[45]

The combination of a TZD and metformin has previously been associated with a 48% relative risk reduction in mortality in diabetic patients within 1 year of an acute MI.[46] Alogliptin/pioglitazone is the only fixed dose combination of a DPP-4 inhibitor and an insulin sensitiser. It may offer significantly greater glycaemic control than the two therapies separately. In a 26-week, double-blind, parallel group study, HbA1c was significantly reduced by 1.6% and 1.7% in patients treated with the combination of alogliptin/pioglitazone 12.5/30 mg or alogliptin/pioglitazone 25/30 mg, respectively, versus monotherapy with alogliptin or pioglitazone ($p<0.05$).[47] Furthermore, combining the two therapies and adding them to metformin resulted in a significantly greater and more durable reduction in HbA1c versus metformin plus pioglitazone over 52 weeks.[48] This combination has also been associated with a low incidence of hypoglycaemia and a neutral effect on weight gain over 26 and 52 weeks of treatment, respectively.[48,49] The positive benefit–risk profile of pioglitazone, which includes potent HbA1c reduction, durable glycaemic control, and low risk of hypoglycaemia, outweighs the treatment-associated bone fracture risk.

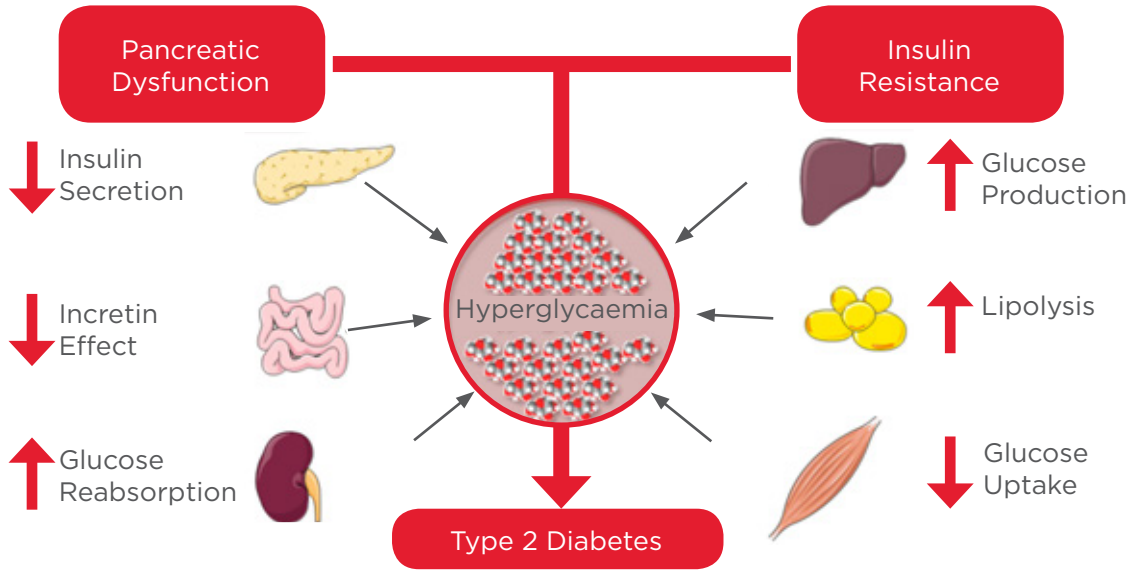

Figure 1: Pathogenesis of Type 2 diabetes - insulin resistance in muscle and liver and impaired insulin secretion represent the core defects in Type 2 diabetes.[1]

The fixed combination of a DPP-4 inhibitor plus pioglitazone may have a complementary mode of action and offer favourable CV outcomes.

The Future Dimension: What do the CV Outcome Studies for DPP-4 Inhibitors tell us?

Professor Kausik Ray

Epidemiological data show that diabetes doubles the risk of coronary artery events and ischaemic and haemorrhagic stroke.[50] Meta-analysis data have demonstrated that more intensive glycaemic control therapy is associated with a 17% relative risk reduction in non-fatal MI and a 15% risk reduction in coronary heart disease, versus less intensive glycaemic control therapy, but it makes no difference to stroke or all-cause mortality.[51] Overall, CV risk reduction requires multiple interventions including blood pressure control and lipid lowering, and although lowering HbA1c may not have as high an impact on CV risk reduction as targeting blood pressure and lipid lowering, it may be an additional beneficial intervention in a high-risk patient population.[51] In support of this, results from UKPDS have demonstrated that reducing HbA1c by 1% results in a 37% reduction in MV endpoints.[52]

Existing anti-hyperglycaemic therapies have several limitations, including the risk of hypoglycaemia, gastrointestinal side-effects, and weight gain. In particular, weight gain associated with these therapies is likely due to increased adiposity, consequent increase in blood pressure, and more atherogenic lipid profiles.[53] In particular, meta-analysis data have shown that SUs are associated with an increased risk of mortality and stroke[54] leading to guidelines from the US FDA requiring CV outcome studies for new antidiabetic agents.[55]

CV outcome studies have been conducted for the DPP-4 inhibitors, alogliptin (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care [EXAMINE]),[56] and saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction [SAVOR-TIMI]).[57] Results have shown that alogliptin significantly reduced HbA1c, but did not increase CV-related mortality, versus placebo in T2D patients with very high CV risk (previous acute coronary syndrome 15–90 days prior to randomisation).[56]

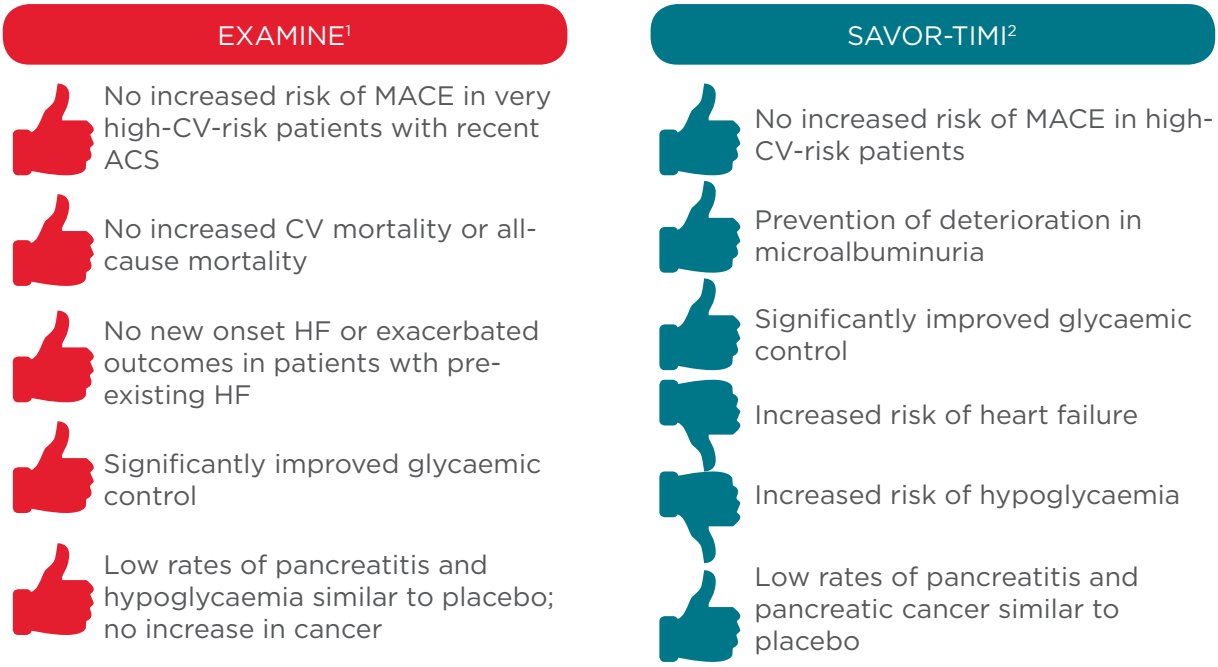

Figure 2: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) and Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) trials: conclusions.

MACE: major adverse cardiac event; ACS: acute coronary syndrome; CV: cardiovascular; HF: heart failure. *White W et al.,[56] Scirica B et al.[57]*

Saxagliptin was associated with superior glycaemic control compared to placebo in a T2D population with a history of CVD or with multiple associated risk factors, and demonstrated non-inferiority to placebo for the primary composite outcome of non-fatal MI, non-fatal stroke, or CV death. Alogliptin had no effect on the *post hoc* composite endpoint of CV death and hospitalisation for heart failure (HF) in patients with or without a prior history of HF. Measurement of N-terminal pro-brain natriuretic peptide, a predictor of HF, after 6 months of alogliptin treatment, revealed a reduction in levels when compared to baseline, although a mechanism for this is yet to be elucidated.[58] In contrast, more patients receiving saxagliptin were hospitalised for HF in comparison to placebo (Figure 2).[57] Although both alogliptin and saxagliptin were able to meet their primary endpoints in these outcome studies, it should be noted that these outcome studies were not designed to demonstrate superiority in CV-protective benefit.

Currently available data from CV outcome studies provide valuable evidence on the CV safety of DPP-4 inhibitors; however, concerns remain about the possibility of increased HF risk. Future DPP-4 inhibitor studies will provide further data on the treatment-associated CV event risk, and consequently aid clinical decisions about treatment intensification.

Symposium Summary

The meeting explored the pharmacology of DPP-4 inhibitors in detail and provided an insight into the structural differences that influence the selectivity and efficacy of the currently available DPP-4 inhibitors. Clinically, DPP-4 inhibitors consistently achieve a reduction in HbA1c, have long-term durability in maintaining glycaemic control, and are associated with a low risk of hypoglycaemia. Furthermore, they are well-tolerated and can be administered as combination therapy. Recent data also indicate that DPP-4 inhibitors do not alter the risk of CV events. The relationship between increased insulin resistance and CV risk was explored. Pioglitazone targets insulin resistance, and therefore – alongside potent HbA1c reduction, durable glycaemic control, and low risk of hypoglycaemia – may offer favourable CV outcomes when provided in combination with DPP-4 inhibitors.

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