REFLECTIONS ON THE SANOFI EASD 2016 SYMPOSIUM

It is truly an exciting time to be working in the field of diabetes. In this newsletter, we review the symposium ‘Facing new horizons: Optimism and opportunities in diabetes management’, held in Munich on 12 September during EASD 2016.

More than 1,500 healthcare providers attended this educational meeting, which was organised by Sanofi and chaired by Professors Jay Skyler (USA) and Ele Ferrannini (Italy). An esteemed faculty harnessed the optimism generated by the proliferation of anti-diabetic treatments, the latest clinical data, and potential future advancements to uncover the opportunities that lie on the horizon of diabetes management.

MANAGING RISK IN CLINICAL PRACTICE: CONSIDERATIONS ACROSS THE METABOLIC CONTINUUM

Professor Carol Wysham (USA) opened the morning session by asking delegates to consider diabetes as a cardio-metabolic disease, and to think of their patients as existing on a metabolic continuum that includes varying levels of dysglycaemia, cardiovascular risk and dyslipidaemia. By describing three patient cases, Professor Wysham showed that, by taking this more comprehensive view of the metabolic continuum and each patient’s risk profile, initial targets and treatment can be individualised and appropriately adjusted as a patient’s disease progresses.

The ability to respond appropriately to different patient profiles and to customise and adjust treatment accordingly is particularly important in order to meet the challenge of adherence to diabetes therapy. Professor Kamlesh Khunti (UK) highlighted how poor adherence to treatment is not only associated with immediate impaired glycaemic control and a long-term increased likelihood of adverse outcomes, it is also associated with higher inpatient costs.1,2 Delegates were challenged to take a more holistic approach to managing diabetes by utilising patient education to improve adherence rates and ultimately glycaemic control. Regarding insulin therapy in particular, delegates were asked to consider how the improved features of the
newer basal insulins (e.g. reduced hypoglycaemia and greater flexibility for patients) may positively impact adherence to insulin therapy and patient quality of life.\(^3\)–\(^6\)

Reducing hypoglycaemia was explored further by Professor Robert Ritzel (Germany), who presented findings from a recent meta-analysis, which analysed hypoglycaemia in patients with type 2 diabetes (T2DM) as a function of HbA1c over 6 months of treatment with the newer basal insulin, insulin glargine 300 U/mL (Gla-300), or with insulin glargine 100 U/mL (Gla-100). Gla-300 demonstrated equivalent glycaemic control to Gla-100, with less nocturnal confirmed (plasma glucose ≤ 70 mg/dL) or severe hypoglycaemia (Figure 1).\(^7\) The reduction in risk was comparable to that seen for Gla-100 versus NPH, he explained.\(^8\) As the risk for hypoglycaemia, glucose variability and reaching glycaemic targets (e.g. HbA1c) are closely related, delegates were invited to think about how broader use of continuous glucose monitoring, even in patients with T2DM, may provide further insights into glucose fluctuations. Additionally, Dr Javier Escalada (Spain) gave consideration to those patient populations who are at an increased risk of hypoglycaemia (e.g. seniors with diabetes, patients with impaired renal function), and presented data supporting the use of Gla-300 in these vulnerable patient subpopulations.\(^9\),\(^10\)*

Professor Kausik Ray (UK) expanded the discussion beyond glycaemic control, describing how a broader view of a patient’s profile should take into consideration the other factors that influence cardiovascular risk in people with diabetes, including high systolic blood pressure, high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol.\(^11\) Delegates were reminded that achieving targets for multiple parameters, including both HbA1c and LDL-C, significantly decreases the morbidity and mortality associated with diabetes and cardiovascular risk.\(^12\)–\(^14\) With this in mind, a new class of lipid-lowering agents, namely PCSK9 inhibitor monoclonal antibodies, may change how we target LDL-C in the future. In particular, it was shown that LDL-C levels are substantially lowered with alirocumab or evolocumab versus placebo in patients already taking statins.\(^15\),\(^16\)

Professor Nick Freemantle (UK) concluded the morning session with a discussion of the utility of real-world results (from both prospective, real-life trials and retrospective analyses) in providing additional and complementary clinical insights beyond those of regulatory, randomised, clinical trials. He provided an overview of the Gla-300 real-life study programme – three large, pragmatically designed, real-life, randomised trials ongoing in the US, EU and Brazil. He emphasised that real-life studies are providing an important addition to the clinical evidence base, providing more understanding of the effect of diabetes treatments and better informing clinical decision making in patient populations underrepresented in regulatory, randomised clinical trials.

CHANGING THE PATH TO GLYCAEMIC CONTROL IN T2DM

Diabetes is a progressive disease with a multi-faceted pathophysiology. Opening the afternoon session, Dr Alice Cheng (Canada) reflected on the multitude of therapies now available, which can target different parts of diabetes pathophysiology. This provides an opportunity to combine therapies, potentially earlier in the course of the disease, in order to reach and maintain glycaemic control for longer. Dr Cheng highlighted how this has led to the advent of fixed combination therapies, either as a fixed dose (single pill combinations) or as a fixed ratio (a single injection of a basal insulin and a GLP-1 receptor agonist). The latter approach provides flexibility in that the dose is titrated according to the insulin dose needed to control fasting plasma glucose. As such, these fixed-ratio combinations can be used in the same way as basal insulin alone.

Professor Julio Rosenstock (USA) and Dr Vanita Aroda (USA) presented data from the Phase III clinical programme of one such titratable fixed-ratio combination, iGlarLixi (Gla-100 and lixisenatide), in patients uncontrolled on oral therapy (LixiLan-O), and patients uncontrolled on basal insulin (LixiLan-L). Together, these data highlighted the superior efficacy of iGlarLixi when compared with its individual components. The substantial HbA1c reductions with titratable fixed-ratio combinations are achieved with no increase in confirmed hypoglycaemia* (including nocturnal confirmed) when compared with basal insulins. Moreover, these agents are associated with weight loss/neutrality compared with the weight gain typically seen with basal insulin, and a marked reduction in the incidence of gastrointestinal side effects compared with GLP-1 receptor agonists alone, likely owing to the slow up-titration of the combination product.

How will these titratable fixed-ratio combinations be used in clinical practice? One pressing question is whether it is better to introduce the combination as an alternative to basal insulin or GLP-1 receptor agonists as a first injectable in the patient uncontrolled on multiple oral agents. This question was explored in a debate between Dr Neil Skolnik (USA) and Professor Rosenstock, who put forward the cases for a step-wise, sequential intensification with individual agents versus simultaneous intensification with a fixed-ratio combination, respectively. Using a patient case (Figure 2), the debate generated a great deal of discussion on the relative merits and limitations of each intensification route, but what is clear is that an individualised approach has to be taken to best suit the needs of the patient.

*Confirmed hypoglycaemia was defined as a symptomatic episode associated with a plasma glucose value ≤3.9 mmol/L (70 mg/dL), or an episode that required assistance or was associated with a plasma glucose value ≤3.1 mmol/L (56 mg/dL), irrespective of symptoms. Confirmed hypoglycaemia with onset between 00:01 and 05:59 h was classified as nocturnal.
THE ROAD AHEAD

The final session of the symposium addressed how new data and therapeutic approaches are shaping the future of diabetes care, beginning with a review by Professor Jeff Probstfield (USA) on how the growing body of evidence from cardiovascular outcomes trials is impacting diabetes treatment today. Professor Probstfield suggested that as we move forward, the standard of care adopted for clinical trials as a control intervention must be changed, and that therapeutic guidance for clinical practice will also need to be altered.

Professor Clifford Bailey (UK) discussed the advances being made in the development of several new glucose-lowering agents. These include a depot injection of a GLP-1 analogue that is active for several months, an orally delivered GLP-1 receptor agonist, and hybrid peptides of incretins, glucagon analogues and other peptides that can potentially activate a selection of pharmacological targets with a single injection. Professor Bailey highlighted that – while these and other advances should lead to improvements in glycaemic control and facilitate patient-specific selection of medications – many challenges still confront researchers and clinicians in the quest to reinstate a normally functioning beta-cell population, normal insulin action and normal nutrient homeostasis.

In the final, keynote presentation of the symposium, Professor William Cefalu (USA) reiterated how many advances in the management of T2DM have given rise to an era of optimism. However, he cautioned that, despite these advances, there remain numerous unmet needs that have proved stubbornly resistant to solution. Returning to where the symposium began, delegates were asked to think about what today’s treatment of diabetes should look like if a more comprehensive view of a patient and their diabetes is considered. The message to delegates, which was echoed throughout the course of the day, was that this is a time of an expanding armamentarium of treatments when guidelines are struggling to keep up-to-date with the latest advancements in understanding. Therefore, clinicians need to be educated about the implications of the latest available data, consider the individual circumstances of their patients, and apply a multifactorial and patient-concordant approach to the decision-making process.

During this symposium, many of the issues that patients and clinicians face across the broad metabolic continuum of diabetes and cardiovascular disease were considered. The expert faculty shared their experience and perspectives and invited delegates to think anew about how to help their patients best manage diabetes now and in the future, so that the optimism of today really can be translated into greater opportunities for tomorrow.
REFERENCES


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