Editorial

Biphasic insulin treatment in type 2 diabetes patients

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Type 2 diabetes currently affects more than 20 million people in the United States and 246 million people worldwide. Unfortunately, the prevalence of this global healthcare epidemic is on the rise and it is projected to affect 366 million people in the world by 2030 (1). Type 2 diabetes is a progressive disease, characterized by insulin resistance and inadequate insulin secretion by pancreatic beta cells. After a meal, a reduced first-phase insulin secretion results in postprandial hyperglycemia while an increase in nocturnal hepatic gluconeogenesis causes fasting hyperglycemia. With the progression of beta cell insufficiency, oral drug therapy are insufficient and patients require exogenous insulin supplementation to achieve the recommended glycated hemoglobin target (2). While prandial insulin replaces endogenous first phase insulin secretion, basal insulin decreases the level of fasting hyperglycemia. Commonly, insulin is initiated as a basal dose of a long-acting analogue (insulin glargine or detemir) or prandially using biphasic (premixed) formulations or rapid-acting analogue, although the optimal approach remains controversial (3). Accumulating evidence indicates that control of postprandial hyperglycaemia is also important in achieving HbA_{1c} goals (4); therefore, in some patients, the glycaemic benefits of biphasic or prandial insulin regimens outweigh the risk of hypoglycaemia (more frequent with biphasic or prandial insulin) and these regimens should be positioned as a valid alternative for initial insulin therapy. Moreover, a recent meta-analysis evidences a greater reductions in HbA_{1c} using biphasic or rapid-acting prandial formulations rather than a basal insulin (5). Biphasic insulin aspart 30 (BIAsp 30) is a pre-mixed insulin analog comprising 30% rapid-acting soluble component and 70% long-acting protaminated component to control post-prandial and basal glucose levels, respectively. Randomized controlled trials have demonstrated the safety and efficacy of BIAsp 30 compared with other insulin formulations (including insulin glargine, human insulin, biphasic insulin lispro, and premixed human insulin) (5). In most of the studies examined, the efficacy of BIAsp 30 was evaluated in terms of glycated haemoglobin reduction and/or proportion of patients achieving HbA_{1c} target of <6.5% or <7%, fasting blood glucose, blood glucose profile and/or prandial and postprandial glucose increments. In some studies, efficacy was further evaluated using plasma insulin and glucose infusion rates, plasma C-peptide levels, mean serum fructosamine levels, postprandial hyperlipidaemia, overall well-being, treatment satisfaction and quality of life. Safety was evaluated using physical and laboratory investigations and assessment of incidence of adverse events, including, in many of the studies reviewed, specific evaluation of those events known to be associated with antidiabetic treatment, hypoglycaemia and weight gain. Overall, a strong evidence was provided for better glycaemic control with BIAsp 30 without increases in the incidence of major hypoglycaemia or nocturnal hypoglycaemic episodes. Moreover, weight gain

with BIAsp 30 was minimal and not significantly greater than with basal insulin or BHI 30. Along this line of studies, the international IMPROVE™ observational study investigated the safety profile and effectiveness of biphasic insulin aspart 30/70 (BIAsp 30) in the routine treatment of patients with type 2 diabetes (6). The IMPROVE™ suggested that BIAsp 30 is likely to be cost-effective compared to insulin glargine and biphasic human insulin across a wide range of settings, and under certain circumstances would be a dominant treatment option.

In this issue of *Acta BioMedica*, Giorda et. al published the results from the Italian cohort (7). This cohort included, at baseline, only type 2 diabetic subjects who were using BIAsp 30, according to local regulations regarding observational studies; therefore, their results are quite different compared to the global results. Indeed, after 26 weeks of observation, the patient enrolled showed only a modest, although significant, reduction of HbA_{1c} (-0.63 ± 1.37%, p<0.001), irrespective of baseline treatment (BIAsp 30 alone, BIAsp 30 + OAD, BIAsp 30 + OAD ± insulin), accompanied by a reduction of major and minor hypoglycemic events and a slight weight increase. Moreover, the patients experienced also a reduction of fasting plasma glucose (FPG) and post-prandial glucose (PPG), as expected considering the pharmacokinetic profiles of BIAsp 30. The outcomes did not substantially differ in between subjects ≤65 and >65 years old and the overall treatment satisfaction score increased significantly at the end of the period of observation. The results of the IMPROVE™ study are in accord with previous observational and randomized control trial with BIAsp 30 (5), but the Italian cohort shows a relevant difference: in fact, the lower reduction of HbA_{1c} could be due to the lower initial value of HbA_{1c}, as for FPG and PPG. Furthermore, considering the similar daily dose of BIAsp 30 before and after the observation, the "clinical inertia" could further justify the small reduction of HbA_{1c} and the absence of an increased frequency of hypoglycemic episodes, frequently observed in studies with premixed and/or prandial insulin formulations. However, the more relevant finding, being the study an observational study (absence of randomization and of a treat-to-target approach and the impossibility to prove a causality), is the safety of BIAsp30, rather than its efficacy in reducing overall glucose control (HbA_{1c}), postprandial spikes and overnight hyperglycemia. At the same time, previous randomized clinical trials suggest a greater benefit of using BIAsp30 in subjects with higher BMI and baseline HbA_{1c} (8, 9). Waiting for a trial that specifically addresses this issue, BIAsp 30 seems to be a good, effective and safe choice as initial insulin therapy in type 2 diabetic patient taking OAD and not able to reach a reasonable HbA_{1c} target.

References

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