Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Diabetes & Metabolism 41 (2015) 6S16-6S20

GLP-1 RAs as compared to prandial insulin after failure of basal insulin in type 2 diabetes: lessons from the 4B and Get-Goal DUO 2 trials

F. Porcellati, P. Lucidi, G. B.Bolli*, C. G.Fanelli

Section of Internal Medicine, Endocrinology and Metabolism, Department of Medicine, Perugia University School of Medicine, Italy

Abstract

The add-on of a prandial (short-acting) GLP-1 RA to basal insulin in subjects with T2DM who fail to control A1C on basal insulin, stems from the physiological principles of post-prandial glucose homeostasis, and it is based on evidence from clinical trials. The 4B and GetGoal DUO 2 studies are the first to establish in head-to-head comparison, the efficacy and safety of short-acting GLP-1 RAs *vs* prandial insulin, when added-on to basal insulin glargine. In the 4B study (exenatide 2/d *vs* lispro 3/d) exenatide demonstrated similar efficacy *vs* lispro in reducing A1C to ~7.2%. However, exenatide reduced also body weight and hypoglycemia incidence as compared to lispro. In GetGoal DUO 2, the head-to-head comparison was between lixisenatide 1/d *vs* glulisine either 1/d (at the main meal, basal-plus) or 3/d (basal-bolus). Like in 4B, in GetGoal DUO 2 the A1C decreased to similar values with lixisenatide or glulisine 1/d (~7.2%), or glulisine 3/d (~7.0%). Again, as in the 4B, body weight and hypoglycemia incidence were lower with lixisenatide. In both studies a similar percentage of subjects reached the A1C <7.0% on GLP-1 RA or prandial insulin. A higher percentage of subjects reported adverse events on GLP-1 RAs, primarily gastrointestinal related. The studies 4B and GetGoal DUO 2 suggest that after failure of basal insulin in T2DM, the add-on of prandial GLP-1 RA is as effective as prandial insulin in lowering A1C, with added benefits of reducing body weight and risk for hypoglycemia. In addition, the GLP-1 RA + basal insulin is a simpler therapeutic option as compared to basal-plus and basal-bolus regimens.

Keywords: GLP-1 receptor agonists, exenatide, lixisenatide, basal insulin

1. Introduction

The modern idea of adding-on of GLP-1 RAs in subjects with type 2 diabetes (T2DM) who fail to control blood glucose on basal insulin (± oral agents) [1] stems from the lessons of physiology of post-prandial blood glucose regulation in normal, non-diabetic subjects.

In physiology, the post-prandial plasma glucose is highly controlled by multiple, integrated mechanisms which cooperate to limit excursions of plasma glucose above 120-130 mg/dL [2]. Teleologically, this suggests the importance in nature of preventing even small increase of glucose after meals to avoid the cascade of metabolic, endothelial and vascular, deleterious consequences [3]. In response to a mixed meal, a rapid rise in insulin (initially portal, later systemic as well), combined with an intra-islet paracrine suppression of glucagon, and systemic suppression of free fatty acids by insulin, cooperate to suppress endogenous glucose production and stimulate peripheral glucose utilization. Both these two mechanisms limit the increase of glucose in plasma. In addition, the meal directly stimulates the acute release of incretin hormones, the two primary being GIP and GLP-1. Indeed GLP-1 stimulates directly insulin secretion in a glucose-dependent manner, suppresses glucagon, either indirectly (*via* pancreatic islet hyperinsulinemia) and directly [4], and decelerates gastric emptying [5]. The latter mechanism reduces the rate of entry of ingested glucose into the circulation, and contributes by at least 50% to the overall incretin effect to reduce post-prandial [6].

Post-prandial hyperglycemia is an early abnormality in the natural history of type 2 diabetes, as a consequence of impaired insulin secretion and relative hyperglucagonemia. However, although it is controversial whether plasma incretin concentrations are reduced in T2DM [7], the overall incretin effect is lower than normal [8]. The recent availability of short-acting GLP-1 RAs, such as exenatide and lixisenatide, used either alone or in combination with oral agents, has made it possible to reduce post-prandial hyperglycemia in T2DM. Hence, the successfully tested hypothesis of adding GLP-1 RAs to reduce post-prandial hyperglycemia also in combination with basal insulin in those T2DM subjects who fail to control blood glucose on basal insulin only (± oral agents) [9-11]. With

***Corresponding author.**
E-mail address: geremia.bolli@unipg.it (G. B. Bolli).

such a combination, A1C decreases, body weight is reduced, and there is no increase in hypoglycemia. These observations have opened the door to a new paradigm treatment, i.e. add-on of prandial GLP-1 RAs in place of prandial insulin after failure of basal insulin to control hyperglycemia and A1C [1].

The initial randomized controlled studies of add-on of GLP-1 RAs to basal insulin have been conducted *vs* placebo [9-11]. More recently, two studies have compared efficacy and safety of exenatide [12] and lixisenatide [13] *vs* prandial insulin, when either of these two GLP-1 RAs is added to basal insulin. These clinically meaningful comparisons have provided a number of relevant informations for the clinical decision as to when, if, and how to add-on prandial insulin or GLP-1 RA to basal insulin in T2DM failing to basal insulin only. In this short review, the 4B and GetGoal DUO 2 studies will be summarized and commented, and its practical messages highlighted.

2. The 4B Study

In the 4B study (Basal insulin glargine + exenatide BID *vs* Basal insulin glargine + Bolus insulin lispro) [12], the efficacy and safety of treatment of post-prandial hyperglycemia with either exenatide twice daily, or insulin lispro at each meal, in T2DM subjects inadequately controlled on titrated insulin glargine and metformin, were compared. This well performed study in a quite large number of subjects (n = 1036 screened, n = 917 enrolled) has several implications for clinical practice. First, the 4B study has examined the common subjects attending the diabetes clinic, i.e. age ~60 years, relatively long (known) diabetes duration (mean 12 years), and poor glycemic control despite treatment with basal insulin glargine and glucose lowering oral agents. Metformin was continued, and sulphonylurea, if any, withdrawn, and titration of insulin glargine optimized for 12 weeks (BIO-phase) before randomization to either exenatide (2/d) or lispro added at each meal (3/d) to glargine. Unfortunately, optimization of basal insulin was insufficient in 4B, since in the three month BIO phase period, the fasting plasma glucose and A1C decreased only from ~150 to ~130 mg/dL, and from 8.5±1% to 8.2±1%, respectively. At the end of this period, there were only 92 "responders" (A1C ≤7.0%) in whom A1C decreased from 7.9±0.7 to 6.7±0.4%, whereas 652 subjects were "failures" (A1C>7.0%) with A1C declining only from 8.6±0.8 to 8.4±0.9%. Interestingly, as compared to failures, the responders to optimization of basal insulin, tended to be younger, to have shorter diabetes duration, lower baseline A1C and fasting plasma glucose, and to use a smaller insulin glargine dose despite similar body weight. The failures were then randomized to add-on with fixed dose (10-20 µg/die based on tolerability), of exenatide twice daily (n = 315) or titrated prandial lispro (n = 312) while continuing insulin glargine (ongoing titration). The difference in A1C change from randomization to end point at 30 weeks between exenatide or lispro added to glargine (the primary outcome of the study) was -0.04 (95% CI: -0.18, 0.11), demonstrating non-inferiority for both margins of 0.4 and 0.3%. At end point of 30 weeks, A1C dropped from 8.3±1.0 to 7.2±1.0% with exenatide, and from 8.2±0.9 to 7.2±1.0% with insulin lispro. Proportions of subjects with A1C ≤7.0% were similar (~50% in both groups). Fasting plasma glucose decreased with exenatide (~11 mg/dL), but not with lispro. Post-prandial PG decreased at all daily meals with both treatments, but to a greater extent with insulin lispro at lunch. As expected, average weight decreased with exenatide (~-2.5 kg) while it increased with lispro (~2.1 kg). Insulin glargine dose was reduced more in the lispro group (~-10 U) vs exenatide (~-5 U). Incidence of hypoglycemia was greater with lispro for minor episodes (41 vs 30% for exenatide) and for confirmed non-nocturnal episodes (34 vs 15% for exenatide). As expected gastrointestinal-related adverse events, including nausea, vomiting, and diarrhea, were more common with exenatide as compared to lispro (47 *vs* 13%, respectively).

The 4B study adds important knowledges on how to progress the treatment of subjects with diabetes who do not meet the target despite basal insulin + metformin.

First of all, as is often the case, in the 4B study [12] we can learn from the results of the period of basal insulin optimization, the BIO phase period. In the total study population, after 3 months of titration of basal insulin, A1C decreased only to ~8.2%, suggesting not adequate titration of basal insulin. Previous studies indicate that when basal insulin is titrated optimally at the target in T2DM subjects, A1C decreases more as compared to what has been obtained in the 4B study [14,15].

As compared to prandial lispro 3 times/d, exenatide (2 times/d), similarly reduced A1C by end of studies by ~1.0% (from 8.2 to ~7.2% with both treatments). Interestingly, this occurred in a similar percentage of subjects ("responders" ~50% in both groups). As said, in 4B the comparison between exenatide and lispro occurred in the presence of suboptimal titration of basal insulin, thus generating the hypothesis that a more aggressive titration of basal insulin would result into even better (lower) A1C by end of the study. Add-on of exenatide to basal insulin was associated with additional benefits vs lispro, such as loss of body weight and lower incidence of non-nocturnal hypoglycemia. As expected, more gastrointestinal related adverse events were seen with exenatide, but apparently this did not translate into treatment discontinuation which did not differ beteween the two arms.

With the limitation of insufficient titration of basal insulin, the 4B study has proven non-inferiority of the prandial GLP-1 RA exenatide vs prandial insulin, thus substantiating the hypothesis that prandial insulin is no longer the exclusive option after failure of basal insulin.

3. The GetGoal DUO 2 study

The GetGoal DUO 2 study results have not been published yet, and therefore the comments are based on the presentation of the trial at the June 2015 ADA meeting in Boston [13]. GetGoal DUO 2 follows the studies GetGoal-L [10] and GetGoal DUO 1 [11], which have both explored the efficacy