Switching From Insulin Bolus Treatment to GLP-1 RAs Added to Continued Basal Insulin in People With Type 2 Diabetes on Basal-Bolus Insulin

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In this issue of *Diabetes Care*, Rosenstock et al. (1) present successful substitution of prandial insulin with the long-acting glucagon-like peptide 1 receptor agonist (GLP-1 RA) albiglutide in the majority of a large group of people with type 2 diabetes (T2D) previously on basal-bolus (BB) insulin. The authors demonstrate that discontinuation of prandial insulin, either in total or in part, with add-on of albiglutide once per week while continuing titrated basal insulin (BI) improves glycemic control similarly to optimization of BB, reduces the risk for hypoglycemia, lowers body weight, and simplifies the insulin regimen, with improved patient-related outcomes. Before this study, the possibility of successful add-on of a GLP-1 RA, either short- (2,3) or long-acting (4,5), as alternative to prandial insulin was demonstrated in people on BI who needed treatment for prandial control. Two relatively small studies reported some advantages with addition of a long-acting GLP-1 RA to maintained BB (6,7), but it was only the FLAT-SUGAR (FLuctuATion Reduction With inSULin and Glp-1 Added togetheR) trial that demonstrated in 102 people with T2D and high cardiovascular risk on BB that the short-acting GLP-1 RA exenatide could fully substitute for prandial insulin (8). However, it was not known whether people already on BB could switch from three daily prandial insulin injections to a weekly GLP-1 RA while continuing BI before the study by Rosenstock et al. (1). If confirmed, these new findings will lead to a change in the treatment paradigm of the presently insulin-treated T2D population, estimated worldwide to be more than 60 million patients (9), at least one-third of whom are likely on BB insulin.

T2D is characterized by variable combinations of impaired insulin secretion and insulin resistance, primarily hepatic. While insulin resistance remains relatively stable over time, the progressive deterioration of β-cell function often worsens hyperglycemia as time goes on, thereby calling for escalation of glucose-lowering treatment. In practice, injectable BI has generally been introduced as a "last step" in the natural history of T2D, usually years after failure of one or more noninjectable glucose-lowering drugs (10). To counter this clinical inertia, timely initiation of BI was proposed (11,12) and recommended (13), but the recent availability of newer glucose-lowering agents, especially GLP-1 RAs and sodium–glucose cotransporter 2 inhibitors, has again postponed the initiation of BI (14). Prandial insulin is not recommended as an early treatment, as even with rapid-acting or ultra-rapid-acting analogs it is a less efficacious glucose-lowering agent than BI in T2D (15,16) and carries greater risk for hypoglycemia and body weight gain (13). Nevertheless, when uncontrolled hyperglycemia develops over time, in common practice it is prandial insulin that is added to BI, and this treatment paradigm remains generally unchanged throughout life. It is to the large population of people with T2D who are "locked" in BB treatment that the study of Rosenstock et al. addresses attention and offers a more convenient, safer, and simpler treatment that is similarly effective.

Rosenstock et al. (1) studied a relevant number of people with T2D with poor glycemic control despite BB treatment and randomized them to either continuation of optimized BB ($N = 412$) or to replacement of prandial insulin with albiglutide once per week added on to titrated BI ($N = 402$). After 26 weeks, both groups achieved similarly good glycemic control, but in the albiglutide-BI group 54% of subjects totally withdrew prandial insulin lispro and 18% continued lispro at a lower dose versus baseline, whereas the remaining 28% had to resume lispro at a dose similar to or higher than baseline. Overall, 72% of subjects who initiated albiglutide no longer needed prandial insulin or used it at a lower dose. Albiglutide added to BI was associated with 24% lower incidence and 57% lower rate of severe and/or documented symptomatic hypoglycemia, a lower body weight by >4 kg, and improvement of

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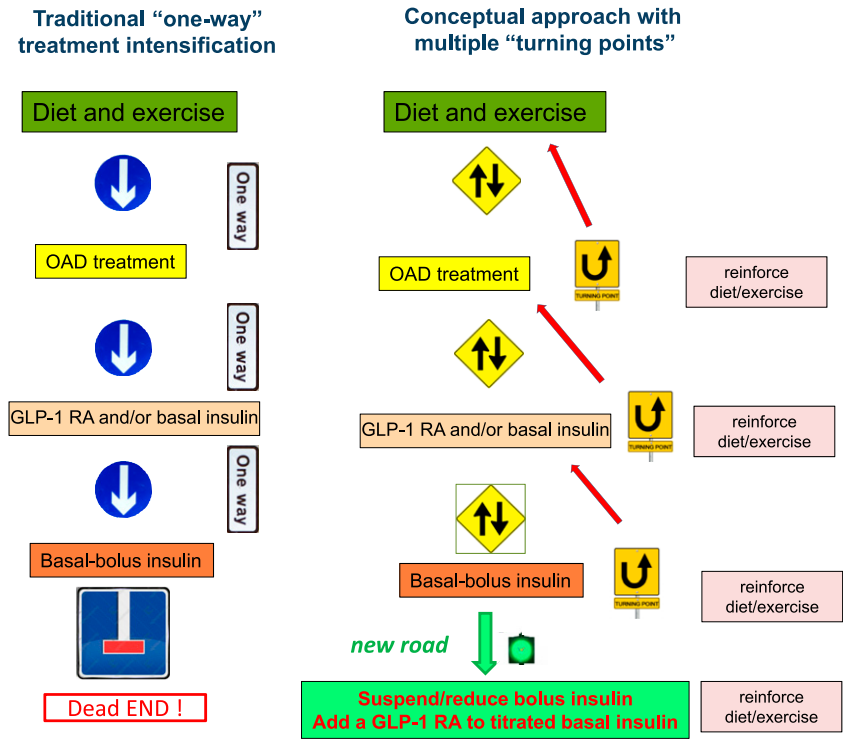

Figure 1—Left: Traditional "one-way" intensification algorithm for treatment of T2D, with basal-bolus insulin regimen as last, irreversible step at the end of the road. Right: the new "multiple turning points" algorithm, where each step may be reversible and the "new road" is proposed, with possible switch from the BB insulin regimen to GLP-1 RA + titrated BI with withdrawal of prandial insulin (in total or in part). OAD, oral antidiabetes drug.

measures of quality of life and fear of hypoglycemia. As expected, gastrointestinal adverse events were more frequent in the albiglutide-BI arm (26% vs. 13%), with slightly greater study discontinuation than BB (3.5% vs. 2.2%).

In many ways, this study marks a paradigm shift in the treatment of T2D. It is still commonly accepted that treatment escalation in patients with T2D follows a "one-way road" that ultimately leads to BB (Fig. 1, left panel). Instead, diabetes treatment should be considered as a multilane road with several possible junctions and turning points. This applies, as originally demonstrated by Rosenstock et al., to the de-escalation from BB, but it may also apply to all other steps in the treatment algorithm (Fig. 1, right panel). In this regard, it is noteworthy that reductions in the number and doses of glucose-lowering drugs can also be accomplished by intensive lifestyle modification at any stage of the disease.

While the study by Rosenstock et al. also reinforces recent guidelines and consensus algorithms that have de-emphasized the role of rapid-acting insulin in the management of T2D, it is important to note that in a certain subgroup of patients, prandial insulin supplementation is still unavoidable. This is supported by the fact that despite the addition of albiglutide, 46% of patients still required prandial insulin supplementation. Interestingly, Rosenstock et al. could not predict the absolute need for prandial insulin by baseline characteristics, such as diabetes duration, age, weight, HbA_{1c}, or insulin dose, although the effect of duration of BB treatment was not reported. This underlines that beyond standardized treatment algorithms, individualization of diabetes treatment at present still requires clinical judgment and experienced physicians. The hope remains that in the near future treatment stratification may be aided by both patient phenotyping and genotyping.

It is also noteworthy that despite the clear advantages of the GLP-1 RA/BI combination in terms of risk reduction of hypoglycemia, weight loss, and quality of life, similar improvement in glycemic control was also seen in the patients treated with BB. This suggests that in routine clinical practice insulin dose intensification, both basal and prandial, is often not performed with sufficient stringency, as several "real-world" studies indicate. However, in real-world clinical practice, similar limitations and treatment inertia also apply to the combination of BI and GLP-1 RA, with insufficient titration of BI and poor adherence to GLP-1 RAs. Therefore, it remains to be shown whether the impressive glycemic results of the experimental trial by Rosenstock et al.—both in the BB insulin group and in the GLP-1 RA/BI group—can readily be translated into clinical practice.

Limitations in the study of Rosenstock et al. include the relatively short duration of the study (26 weeks); only 1 month of optimization of the BB regimen before randomization of patients with poor glycemic control, with need to continue titration of BI after initiation of albiglutide, thus masking the response to albiglutide; and the fact that albiglutide is currently not available for treatment and similar effects still must be shown with other long-acting GLP-1 RAs that are commercially available, such as liraglutide (17), dulaglutide (18), and semaglutide (19).

Among the many interesting questions raised by the study of Rosentock et al. is the effect of replacing prandial insulin therapy with a short-acting GLP-1 RA. This was the case in the FLAT-SUGAR trial, where exenatide was used two or three times per day in 56% and 44%, respectively, of subjects with T2D. Short-acting GLP-1 RAs have somehow a different mechanism of action compared with long-acting GLP-1 RAs, since they primarily reduce postprandial glycemic excursions by slowing down gastric emptying with only modest or absent stimulation of endogenous insulin secretion (20–22). This is different from the effects of long-acting GLP-1 RAs, such as albiglutide in the study of Rosenstock et al. (1), which sustain endogenous insulin secretion in the fasting and prandial state driven by hyperglycemia (20–22). Short-acting GLP-1 RAs appear more attractive for the physiological mechanism of action as an add-on to BI but require multiple mealtime administrations, as compared with only once daily (liraglutide) or weekly dosing of long-acting GLP-1 RAs such as dulaglutide and semaglutide. In theory, the two different fixed-ratio GLP-1 RA/BI combinations (liraglutide/degludec, lixisenatide/glargine U100) might also be tested versus BB. However,

such fixed combinations may not allow for flexible dose adjustments of the two components in individual subjects, who often have different titration needs. Finally, in the study by Rosenstock et al., prandial insulin was halved at the time of albiglutide initiation and completely withdrawn after 4 weeks. In clinical practice, a more gradual reduction of prandial insulin over days or weeks, driven by the subjects' individual glycemic responses to different meals, is likely to be preferable.

Even though switching patients from BB insulin treatment to a GLP-1 RA/BI association appears to be a beneficial option for patients who have not received a GLP-1 RA in the past, it would seem more reasonable to initiate a GLP-1 RA even before adding prandial insulin to BI, especially in those patients with cardiac or renal comorbidities.

Future studies should now possibly identify the clinical characteristics of patients already on BB that have good chances to be responders to a GLP-1 RA/BI association without a need for prandial insulin supplementation, and confirm in real life and long term the good results presented by Rosenstock et al.

The study by Rosenstock and colleagues changes the concept of the "one-way road" of BB in T2D treatment to that of a "multi-lane road" where several junctions and turning points are possible for the benefit of individual patients.

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