Therapeutic strategies for type 2 diabetes mellitus patients with very high HbA1c: is insulin the only option?

Muhammad Abdul-Ghani, Ralph DeFronzo

Division of Diabetes, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Correspondence to: Muhammad Abdul-Ghani, MD, PhD. Division of Diabetes, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, USA. Email: abdulghani@uthscsa.edu.

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Approximately 40% of patients with type 2 diabetes mellitus (T2DM) will experience microvascular complications (1), and T2DM is the leading cause of renal failure and blindness in western countries (2-4). Two landmark studies, the Diabetes Control and Complications Trial (DCCT) (5) and United Kingdom Prospective Diabetes Study (UKPDS) (6), as well as many others (7-9) have documented that hyperglycemia is the major risk factor for microvascular complication and that the risk of developing those complications is directly related to the magnitude of hyperglycemia as measured by the HbA1c. Further, improving glucose control markedly reduces diabetic microvascular risk. Each 1% reduction in the HbA1c is associated with ~40% reduction in the risk of development of retinopathy and nephropathy (5,6). Therefore, maintaining good glycemic control (i.e., HbA1c <7.0%) while preventing microvascular complications is the mainstay of management of T2DM as well as T1DM and is recommended by all professional organizations (10).

Despite the irrefutable evidence of the importance of adequate glycemic control in reducing microvascular risk, approximately one half of T2DM patients fail to achieve the recommended American Diabetes Association (ADA) goal of glycemic control, i.e., HbA1c <7.0% (11,12). Further, several studies have reported that 10–15% of T2DM patients in the US and elsewhere manifest HbA1c >9.0% (13,14), rendering them at very high risk for microvascular complications.

Because T2DM is lifelong disease, adherence to antglycemic therapy is essential for the achievement of long-term glycemic control. Multiple studies have demonstrated that more than half of T2DM patients discontinue their antihyperglycemic medications within 12 months of initiating therapy (15,16), and this discontinuation rate is even higher amongst patients receiving injectable agents, e.g., glucagon-like peptide-1 receptors agonists (GLP-1 RA) (17). Thus, improving adherence to antihyperglycemic therapy is an important unmet need in the management of T2DM. The study by Henry and colleagues (18) examined the impact of a novel drug delivery system, ITCA 650, on glucose control in T2DM patients with very high HbA1c (mean =10.8±0.7, range, 10–12%). ITCA 650 is an osmotic pump of matchstick size which is placed underneath the skin and continuously delivers exenatide at a predetermined constant rate for 6–12 months. Placement of the device takes 10–15 minutes and involves a simple procedure that can be performed in the clinic under local anesthesia. Thus, once the device is placed, it ensures 100% adherence to therapy for the 6–12 months treatment period.

Henry and colleagues (18) enrolled sixty poorly controlled T2DM patients with HbA1c 10–12% who did not qualify for the placebo-controlled trial because the baseline HbA1c was >10% and a placebo-controlled study in this group was felt to be unethical. Other than diabetes, patients were in good general health and treated with lifestyle alone or lifestyle plus metformin with or without sulfonylurea. The ITCA 650 device that delivers 20 µg/day...
was implanted for 13 weeks, at which time the device was replaced with another which delivered 60 µg/day for additional 26 weeks.

The primary outcome of the study was the decrease in HbA1c from baseline to week 39. Rescue therapy was allowed in patients in whom the HbA1c did not decrease below 8.5% at week 26. Fifty-two (86.7%) patients completed the study. Six patients withdraw consent because of adverse events and two patients were lost to follow-up.

The mean decrease in HbA1c at 39 weeks was 2.8%. Approximately half of the patients experienced >3% reduction in HbA1c, and one quarter experienced >4% decrease in HbA1c. Moreover, despite very high initial HbA1c (HbA1c >10%), approximately one quarter of patients achieved the ADA goal for glycemic control (i.e., HbA1c <7.0%) at 39 weeks. The reduction in HbA1c produced by ITCA 650 is impressive when considering that 20% of participant were able to discontinue their baseline antihyperglycemic therapy and remain on exenatide monotherapy. Two factors contribute to the robust decrease in HbA1c. First, it is very well established that the higher the starting HbA1c, the greater is the decrease in HbA1c with all antidiabetic agents. Second, the GLP-1 RA are intrinsically potent glucose lowering agents and correct 6 components of the ominous octet (19,20). Further, as pointed out by the authors, a major advantage of the ITCA 650 is that 100% adherence to therapy is ensured by ITCA 650 and this is rarely/never has been achieved in other clinical studies with injectable (daily or weekly) GLP-1 RA. Not pointed out by the investigators, however, is the potent rapid onset and durable effect of GLP-1 RA to reduce the HbA1c. This only can be achieved by improving beta cell function which is essential in providing durable reduction in HbA1c. Thus, normalization of beta cell function has been shown within 8 hours after a single injection of lixisenatide (21) and persisted for up to 3 years with exenatide (22).

Despite the impressive decline in HbA1c (2.8% decrease), the resultant HbA1c on mean would be ~8.0% which still is above the goal recommended by the ADA/European Association for the Study of Diabetes (EASD). However, the good news is that addition of a single oral antidiabetic agent, pioglitazone (23) or sodium/glucose cotransporter 2 (SGLT2) inhibitor, is likely to further reduce the HbA1c to the ADA goal of <7.0%.

Most clinical guidelines (10) recommend that T2DM patients with a HbA1c >10% be started on insulin therapy, especially if symptoms (polyuria, polydipsia, nocturia and weight loss) symptoms of hyperglycemia are evident. However, this recommendation more is based on “expert opinion” than on objective evidence. The results of Henry et al. (18) demonstrate that ITCA 650 provides an alternative therapeutic option for patients with a HbA1c between 10–12%. Further, the results of Henry et al. are consistent with a previous study from our group (23) which demonstrated that combination therapy with exenatide plus pioglitazone produced an even greater decrement in HbA1c (~4.8%) in T2DM patients with a baseline HbA1c =10–16% (mean HbA1c =11.4%). Further, the decrement in HbA1c produced by exenatide plus pioglitazone was significantly greater than that produced by basal/bolus insulin (4.8% vs. 3.8%, P<0.001), and more patient achieved the ADA goal of glycemic control with exenatide plus pioglitazone (70% vs. 35%, respectively, P=0.003). Collectively, these results (18,23) suggest that a GLP-1 RA alone or in combination with pioglitazone provide a very effective therapeutic option alternative to insulin for glucose control in patients with a HbA1c >10%. A major advantage of combined exenatide/pioglitazone therapy is that these agents “normalize” glucose metabolism by correcting 7 of the 8 Ominous Octet including the two major core defects, insulin resistance and beta cell failure present in T2DM patients (19,24-26).

Although ITCA 650 was very effective in improving glycemic control, its effect on body weight was modest, 1.2 kg and it did not reach statistical significance. This result is surprising and is in contrast with other studies which have examined the effect of GLP-1 RA monotherapy, including exenatide, on glucose control in T2DM. These studies consistently have reported significant weight loss in the range of 3–5 kg over 52–104 weeks (27,28). Because participants in the study had very poor glycemic control (HbA1c =10–12%), it is likely that many patients had a mean day long plasma glucose concentration that was well above the threshold for renal glucose excretion (29). The robust reduction in HbA1c would have been expected to markedly reduce glucosuria, thereby, reducing urinary caloric loss and offsetting the intrinsic action of the GLP-1 RA to promote weight loss. Measurement of urinary glucose excretion before, during, and at the end of exenatide therapy could have added insight about the impact of ITCA 650 on energy balance and body weight in T2DM patients with very high initial HbA1c.

Lastly, the safety profile of ITCA 650 was consistent with that of other GLP-1 RAs (27,28). Other than nausea, no other drug related adverse events were reported. And, similar to other GLP-1 RAs, the nausea was transient, and
was observed in only ~20% of patients at the initiation of treatment and at 13 weeks when exenatide dose was escalated to 60 µg/day.

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Footnote
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References
20. Abdul-Ghani M, DeFronzo RA. Is It Time to Change the Type 2 Diabetes Treatment Paradigm? Yes! GLP-1 RAs Should Replace Metformin in the Type 2 Diabetes


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