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CASE SERIES

Is insulin degludec a more effective treatment for patients using high doses of insulin glargine but not attaining euglycemia? Some case reports from India

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Binayak Sinha[1]
Kalyan Kumar Gangopadhyay[2]
Samit Ghosal[3]

[1]Department of Endocrinology, AMRI Hospital, [2]Department of Endocrinology, Fortis and Peerless Hospital, [3]Nightingale Hospital, Kolkata, India

Abstract: Insulin therapy is not without side effects. In patients with complications on complex regimens, failure to attain adequate glycemic control exposes the patient to high risks and the considerable mental distress associated with failed injectable therapy. As clinicians, we felt it necessary to undertake a trial of newer therapies like insulin degludec, which according to published literature, appears to be superior to earlier basal analogs by fewer hypoglycemic episodes, better glycemic predictability, and genuine 24-hour coverage. Here we report on three cases seen in our own clinical practice where insulin degludec was used in patients experiencing inadequacies with their current basal insulin therapy (insulin glargine). Switching to insulin degludec resulted in clinically meaningful reductions in hypoglycemia, along with reduced fasting plasma glucose and glycosylated hemoglobin and improved satisfaction with treatment. We also explored the use of long-acting insulin in renal failure and the possibility of dose reduction when switching from existing basal insulin therapy.

Keywords: insulin, glargine, degludec, hypoglycemia

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Introduction

Physiological release of insulin from pancreatic β-cells is characterized by background basal insulin release throughout the day, with additional release of insulin in response to meals (prandial insulin release). Type 2 diabetes mellitus (T2DM) is characterized by progressive loss of this β-cell function, with many T2DM patients requiring insulin supplementation by 7–10 years after diagnosis.[1] Most published guidelines recommend initiation on once-daily basal insulin, with intensification using multiple doses of insulin as the disease progresses.

Long-acting (basal) insulin analogs were developed to provide a more physiological pharmacokinetic/pharmacodynamic profile compared with human insulins, with the aim of being able to administer injections once daily.[2] Despite this, up to 40% of patients on insulin glargine still require twice-daily injections, because the action of the currently available basal insulins, namely glargine and detemir, do not last for 24 hours in some patients.[3–5] In addition, there is some evidence suggesting that splitting the insulin dose into two smaller components if a dose larger than 30 units per day is needed helps in controlling blood glucose.[6] This clearly increases the number of injections required, thereby inconveniencing patients further.

Insulin degludec has arrived with the promise of a more predictable and longer duration of action than that of the existing basal insulin analogs. On this

Correspondence: Binayak Sinha
AMRI Hospital, JC- 16 &17, Salt Lake City, Kolkata, West Bengal 700098, India
Tel +91 9830096410
Email binayak.sinha@gmail.com

background, we report on three patients in whom glargine was replaced with degludec, with impressive results.

Case 1

A 64-year-old obese male who had been diagnosed with T2DM 12 years earlier was doing well on metformin and a sulfonylurea. Four years previously, his glycosylated hemoglobin (HbA_{1c}) had increased to 8.0% and he was also found to have elevated blood pressure. Routine annual examination revealed microalbuminuria and mild nonproliferative diabetic retinopathy. His estimated glomerular filtration rate (eGFR) was 50 mL/min/1.73 m^2. Modification of his antihyperglycemic regimen by addition of insulin glargine (titrated to 40 units at bedtime) resulted in a reduction in HbA_{1c} to 7.3%.

He discontinued all glucose-lowering medications abruptly in October 2013 and was admitted to hospital in a state of stupor. His capillary plasma glucose was high (>600 mg/dL) and there was evidence of dehydration and complete renal shutdown (serum creatinine 7.2 mg%; calculated eGFR 8 mL/min/1.73 m^2), both of which improved with intravenous insulin and fluids (serum creatinine 3.2 mg/dL; eGFR 20 mL/min/1.73 m^2). His antidiabetic regime was subsequently converted to a basal bolus regimen with insulin aspart and insulin glargine. However, after a couple of days, his plasma glucose remained uncontrolled even with 26 units of aspart before breakfast, lunch, and dinner and 50 units of glargine at bedtime. Fasting plasma glucose was persistently above 250 mg/dL. After further dose escalation, reasonable glucose control was achieved with 36 units of aspart before each meal and a split dose of glargine (28 units at 10 am and 50 units at 10 pm). Seven days after discharge, his fasting blood sugar values started fluctuating between 50 mg/dL (symptomatic hypoglycemic episodes) and 156 mg/dL. Meanwhile, his prandial insulin requirement came down to 20 units before each meal. In view of the difficulty in dose titration, his basal insulin component was switched to degludec. His new regimen was aspart 20 units before each meal and degludec 40 units at bedtime (a dose-to-dose shift was not made as per the package insert in view of his advanced nephropathy). After 10 days, he was maintaining a fasting plasma glucose in the range of 112–117 mg/dL and a post meal (lunchtime) glucose of 160–170 mg/dL on linagliptin 5 mg, aspart 26 units before lunch only, and degludec 38 units at bedtime. There have been no further episodes of hypoglycemia.

Case 2

A 52-year-old woman with T2DM for 15 years underwent renal transplantation 3 years prior to presentation for diabetic nephropathy and remained dialysis-free. However, she now has recurrent urinary tract infections, which has been partly attributed to poor glycemic control. She has a body mass index of 35 and a sedentary lifestyle. Her diabetes medication consists of insulin aspart 40 units before breakfast, 50 units before lunch, 40 units before dinner, and insulin glargine 80 units at bedtime, in addition to glimepiride 4 mg, metformin 2,000 mg, linagliptin 5 mg, and acarbose 300 mg per day. Her capillary glucose monitoring at home revealed a mean glucose of 205 mg/dL (fasting), 270 mg/dL before lunch, and 320 mg/dL before dinner. She also complained of burning at the site of glargine injection. It also seemed that the effect of glargine was not persisting for the full 24 hours, as highlighted by raised glucose levels before dinner. Therefore, glargine was replaced by degludec at the same dose. Surprisingly, by day 7, her glucose profile seemed to be much improved, with a mean capillary glucose reading of 150 mg/dL before breakfast, 180 mg/dL before lunch, and 180 mg/dL before dinner. Although her glycemic control needs to be improved further, the patient was pleased that her glucose levels had decreased to below 200 mg/dL for the first time. She was also happy that the injection site pain had resolved.

Case 3

A 64-year-old lady was referred with an HbA_{1c} of 9.2%. A diabetic for 16 years, she had been struggling with her metabolic control for the last one and a half years using lispro 28 units before each meal with glargine 30 units at night and 24 units in the morning. She was taking sitagliptin 100 mg/day but was intolerant to metformin in any formulation. She was also on losartan 50 mg twice daily for documented microalbuminuria and on atorvastatin 10 mg once daily for dyslipidemia. She had no history of macrovascular events and there was no evidence of retinopathy on retinal screening 3 months earlier. On examination, her body mass index was 29.6 and her blood pressure was 132/78 mmHg. Her home blood glucose readings, which she monitored obsessively, showed readings of 184–225 mg/dL before meals and 212–293 mg/dL after meals. She felt depressed at being unable to control her blood glucose in spite of her best efforts and wanted to at least reduce the number of insulin injections she was taking. Therefore, she was converted to lispro 20 units before meals along with

degludec 30 units at bedtime daily, with plans to uptitrate according to her readings. She returned for review after 3 weeks with premeal readings of 70–116 mg/dL and postmeal readings of 136–172 mg/dL. In fact, she had reduced her degludec dose to 26 units after she recorded two fasting glucose readings of 78 mg/dL and 73 mg/dL on consecutive days. She has had no hypoglycemia. Her most recent HbA_{1c} 2 months after starting this new regimen was 7.6%.

Discussion

All three patients presented here had had diabetes for a long period of time and had poor β-cell reserve. They had complications from diabetes and attaining at least a modest glycemic control was a necessity. All had poor glycemic control in spite of high doses of insulin and oral antidiabetic agents as well as adequate adherence to lifestyle measures and therapy. Pain at the injection site was definitely a problem in one of these patients, and the need to inject basal insulin twice daily was evident in all cases. In this situation, the decision to replace insulin glargine with insulin degludec not only brought about a marked improvement in glycemia, but provided much needed relief to the patient in the form of a reduced number of injections and a decrease in injection site pain. In two of these patients, a reduction in dose requirement was also seen.

Insulin degludec is a new-generation ultralong-acting basal insulin analog that has recently been approved for use. Upon subcutaneous injection, it forms multihexamers, resulting in a soluble depot in the subcutaneous tissue from which monomers gradually separate.[7,8] This mechanism provides slow and continuous absorption, leading to a flat, ultralong pharmacokinetic profile and a four–fold less variable glucose-lowering effect compared with insulin glargine.[9] The duration of action extends beyond 42 hours and it has been studied across the spectrum of diabetes in a large clinical trial development program, ie, the BEGIN® trials, involving more than 11,000 subjects from 40 countries and encompassing a multitude of ethnic populations.[10]

Seven randomized, controlled, open-label, Phase IIIa treat-to-target trials (26 or 52 weeks) have compared degludec versus glargine (two trials in type 1 diabetes and five trials in type 2 diabetes). Results from all seven trials show noninferiority of degludec over glargine in HbA_{1c} reduction. However, degludec consistently lowered fasting plasma glucose more than glargine. The mean total daily insulin dose to attain a similar HbA_{1c} was also consistently lower with degludec in comparison with glargine.[11–18]

A very recent post hoc meta-analysis compared the within-subject variability in mean blood glucose using 9-point self-measured blood glucose (9P-SMBG) profiles. Interestingly, within-subject variability in mean 9P-SMBG was significantly lower for degludec when compared with glargine (−10% in insulin naïve, −7% on previous oral drugs).[19] These results reinforce the findings of a four-fold lower variability of degludec compared with glargine in pharmacokinetic studies.

As is evident in the present series, the results from clinical trials were replicated in this real world scenario in the form of less insulin requirement, less hypoglycemia, less glycemic variability and a better 24-hour coverage. All these advantages translated into better overall glycemic control.

It may be too early to comment on the long-term efficacy of insulin degludec, but the results from the initial few months seem to be encouraging. Insulin degludec does hold promise, even in refractory cases, and represents a new approach to basal insulin therapy that extends the achievable balance between efficacy and tolerability beyond that possible with current basal insulins. The likely major clinical impact at this stage seems to be a further reduction of hypoglycemia risk, reduced glycemic variability, and a possible reduction in dose when converting from other basal insulins.

Disclosure

BS and KKG have received speaker fees from Eli Lilly, Novo Nordisk, Sanofi-Aventis, and MSD. BS has received speaker fees from BMS-AZ and Novartis. SG has received speaker fees from BMS, Novo Nordisk, and Novartis. The authors report no other conflicts of interest in this work.

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