CASE REPORT

Successful glycemic control with three times a week degludec injection by medical staff for an elderly hemodialysis patient with type 2 diabetes

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Abstract For elderly hemodialysis patients with diabetes, the treatment options are restricted, and insulin therapy plays an important role. However, sometimes it might be difficult for them to inject insulin by themselves because of technical and/or social problems. The recently introduced basal insulin analog degludec has a longer half life than the previous basal insulin analogs such as glargine or detemir. Here we report an elderly hemodialysis patient with type 2 diabetes who was successfully treated with insulin degludec injection by the medical staff at every hemodialysis clinic visit. Throughout this treatment, he did not experience any side effects due to degludec, including hypoglycemia. There are few reports of using degludec for HD patients. In addition, this is the first report showing the validity of a three-times-a-week degludec regimen as a basal supported oral therapy for a hemodialysis patient with diabetes who could not inject insulin by himself. The inferiority of the three-times-a-week degludec regimen compared with the once-a-day glargine regimen in non-hemodialysis patients has already been reported. Based on this, this three-times-a-week degludec regimen should also not be considered as a standard regimen in hemodialysis patients. However, this three-times-a-week degludec regimen may be useful as an alternative for hemodialysis patients who cannot inject insulin once a day by themselves to achieve good and safe glycemic control, improving the prognosis and avoiding problems with hyperglycemia.

Keywords Diabetes · Degludec · Hemodialysis · Elderly · Glycemic control · Basal supported oral therapy (BOT)

Introduction

Patients with diabetes are aging as the world's population ages [1–3]. Elderly patients with diabetes have specific problems. Some oral drugs, such as sulfonylurea compounds, thiazolidinediones and biguanides, carry the risk of hypoglycemia and other possible side effects, such as fluid retention, decreasing bone density and development of lactic acidosis. These may argue against their use in elderly patients [1]. Sometimes it is difficult to introduce insulin to elderly patients because of both the technical problems associated with insulin injection as well as self-monitoring of blood glucose (SMBG) and the social problems associated with living alone or dementia. Diabetes is a risk factor for dementia, and hypoglycemia can worsen dementia. At the same time, dementia increases the frequency of hypoglycemia [2–5]. In the treatment of elderly patients with diabetes, it is necessary to avoid both hypoglycemia and serious acute hyperglycemic emergencies such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) [6].

The number of patients on hemodialysis (HD) is increasing [7, 8], and diabetes is the most common cause of end-stage renal disease (ESRD) in the world [8, 9]. It has been reported that improvement of glycemic control is significantly associated with a lower risk of mortality in hemodialysis patients with diabetes who have no preexisting cardiovascular disease (CVD) [10]. As the treatment option for diabetes in HD patients is restricted [8, 11], insulin therapy may play a key role.

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Table 1 This patient's profile and laboratory data at the first hemodialysis (HD) session in our clinic (foot note)

Profile				
Laboratory data		Reference range		
Age	69 years old	Hemoglobin (g/dl)	10.0	13.6–18.3
Sex	male	Serum albumin (g/dl)	3.9	3.7–5.5
Duration of diabetes	10 years	Serum glucose (mg/dl)	96	
Duration of HD	1 month	HbA1c (NGSP) (%)	4.9	
Dry weight	50.2 kg	HbA1c (IFCC) (mmol/mol)	30	
Body mass index	19.1	Glycated albumin (%)	27.1	11.6–16.4
Retinopathy	PPDR ^a	Postprandial CPR ^b (ng/ml)	4.6	
Neuropathy	Exist	Total cholesterol (mg/dl)	138	150–219
Macroangiopathy	No	TSH (μIU/ml)	3.9	0.4–4.0
Family	live-alone	Free T4 (ng/ml)	1.00	0.8–1.9
Cognitive function	HDS-R 25 pts			
Self-injection of insulin	not available			

^a Proliferative diabetic retinopathy with the retinal laser photocoagulation and the vitreous surgery performed before

^b Postprandial C-peptide immunoreactivity (CPR) was examined about one month after the first HD session, before starting degludec

The recently introduced long-acting insulin analog degludec has unique characteristics: its half life is about 25 h in non-HD patients [12], and its blood glucose-decreasing effect lasts more than 42 h [13]. It has been reported that degludec's pharmacokinetic parameters are not influenced by renal function and hemodialysis [14]. As far as we know, however, there are no other reports on using degludec for HD patients.

Here we report a case of an elderly hemodialysis patient with type 2 diabetes who could not inject insulin by himself because of reduced cognitive function and the physically disabled fingers of his left hand. He had no family members who could inject insulin for him. Considering these social problems, we considered that the medical staff could inject insulin during his visits to the HD clinic. We succeeded in treating him with the long-acting insulin analog degludec three times a week as basal supported oral therapy (BOT). His glycemic control improved without any hypoglycemic episodes.

Case report

A 69-year-old male with type 2 diabetes and chronic renal failure due to diabetic nephropathy was referred to our clinic for maintenance HD treatment after the introduction of HD on admission. Although he had preproliferative diabetic retinopathy, for which vitreous surgery in addition to retinal laser photocoagulation had been performed, he had no problem seeing. As one of the manifestations of diabetic neuropathy, the coefficient of variation of R-R intervals (CVR-R) in the electrocardiogram decreased to 1.76 %. In contrast, he had neither significant coronary artery stenosis as evaluated by coronary angiography

(CAG) nor other macroangiopathies. He lived alone and sometimes forgot to take his medicine. Although he did not meet the criteria for dementia in the point of the score of the Revised Hasegawa Dementia Scale (HDS-R) (Table 1), he showed decreased cognitive function, judging from his behavior in everyday life. First, we planned to treat his diabetes with a dipeptidyl peptidase-4 inhibitor, vildagliptin 100 mg per day, as his previous doctor had, but found that the HbA1c and glycated albumin (GA) values determined at the first HD session at our clinic were 4.9 % (30 mmol/mol) and 29.2 %. Hearing from the patient again, it turned out that he had been treated with some kind of insulin at 4 units per day until several months before, when he had stopped using it for an unknown reason. Two months later, his glycemic control worsened with values of HbA1c 7.9 % (63 mmol/mol) and GA 44.2 % (Fig. 1a). Until that time, his consciousness had been clear without any hyperglycemic emergencies such as DKA or HHC. We tried to restart insulin treatment, but hesitated because he lived alone and had physically disabled fingers of his left hand. In contrast, he was able to take medicine by himself if it was packed together in one package. We decided to add voglibose 0.6 mg and mitiglinide 10 mg to vildagliptin 100 mg per day and started to let him check his blood glucose (BG) levels both before and after each HD session (Fig. 1a). In spite of the additional drugs, the BG levels before HD were still high, around 252 mg/dl (14 mmol/l) for 4 weeks. Then, we increased the mitiglinide dose up to 20 mg per day. At the same time, we decided to start the long-acting basal insulin analog degludec as BOT. Insulin degludec was injected [4 units (0.8 units/kg)] only after HD, three times a week, by the medical staff because the patient was not able to inject insulin properly by himself in

Fig. 1 The clinical course of HbA1c, glycated albumin and the average of monthly blood glucose (BG) levels before and after HD (a) and the CGM data after 12 months (b). The vertical dashed line indicates the timing when degludec was started. (a, upper) The solid line indicates the HbA1c levels, and the broken line indicates the glycated albumin levels. (a, lower) The next HD session after the first degludec injection was counted as the first day, and BGs were examined before (solid line) and after (broken line) each HD session. The average of these BGs was calculated for each month. The data at month 0 reflect the averages of BGs for 1 month before starting degludec. Degludec had been increased gradually since the beginning of the 9th month, while oral hypoglycemic agents were continued at the same dose after starting degludec. **b** The CGM by iPro2® was performed after 16 months. The minimum glucose level was 94 mg/dl, and the average glucose level was 141 mg/dl for a total of 78 h. Hypoglycemia was not detected during CGM. Because the patient could hardly perform SMBG for the revision of CGM at home, almost all SMBGs were done at the clinic. Because of the deficit of the SMBG data at home, the CGM data were interrupted for about 20 h

spite of repeated technical instructions. The BG levels before and after HD improved gradually (Fig. 1a), and the BG levels before HD dropped under 180 mg/dl (10 mmol/l) after the fourth degludec injection. Three months later his average BG levels before and after HD improved to 142 mg/dl (7.89 mmol/l) and 136 mg/dl (7.54 mmol/l) each, and HbA1c and GA also improved to 6.1 % (43 mmol/mol) and 20.0 %, respectively. This improved

glycemic control was maintained for at least 6 months without any hypoglycemic episodes or other side effects of degludec. Seven months later, the BG levels before HD started to rise gradually, followed by an increase of the HbA1c and GA levels. The dose of degludec was gradually increased up to 8 units per HD session 10 months later (Fig. 1a). Twelve months later, the average BG levels before HD, HbA1c and GA improved to 167 mg/dl

(9.28 mmol/l), 5.7 % (39 mmol/mol) and 20.5 %, respectively, without any hypoglycemic episodes. Sixteen months later, the postprandial CPR was 7.2 ng/ml, and the dry weight increased up to 53.2 kg (BMI 20.2, +5.9 %), suggesting that his nutritional state had improved. We performed continuous glucose monitoring (CGM) using iPro2® (Medtronic) to elucidate whether asymptomatic hypoglycemia occurred or not. The average and minimum glucose levels were 161 mg/dl (8.94 mmol/l) and 94 mg/dl (5.22 mmol/l) each for the total 78 h (Fig. 1b), supporting that safe glycemic control was maintained.

Discussion

We report successful treatment with three-times-a-week insulin analog degludec injection by the medical staff to an elderly hemodialysis patient with type 2 diabetes. As far as we know, this is the first report showing the validity of using the degludec three-times-a-week regimen as BOT for a hemodialysis patient with type 2 diabetes who could not inject insulin by himself.

Data have been provided by a phase 3 trial in which the insulin degludec three-times-a-week regimen was compared with the insulin glargine once-a-day regimen in insulin-naïve non-HD patients with type 2 diabetes [15]. The result showed inferior glycemic control and increased risk of hypoglycemia with the degludec three-times-a-week regimen compared with the glargine once-a-day regimen. This suggests that the degludec three-times-a-week regimen should not be recommended as a standard regimen and that the degludec three-times-a-week regimen should only be considered as an alternative regimen when a standard regimen cannot be adopted.

Renal impairment is known to decrease the clearance and degradation of circulating insulin [16], meaning that the half-life of insulin could be extended in case of renal failure. Taking advantage of these characteristics in ESRD patients, in spite of having no available pharmacokinetic data about glargine, three-times-a-week basal insulin therapy has been tried for HD patients with diabetes using neutral protamine hagedorn (NPH) insulin or glargine [17, 18]. The glycemic control of all 11 patients in the two studies seemed to improve without severe hypoglycemic symptoms. However, Bouchi et al. pointed out the limitation of their study by describing that the glargine three-times-a-week regimen improved glycemic control for about 24 h but not 48 h after the administration of glargine based on their blood glucose monitoring data [18]. In our case, showing significant hyperglycemia in spite of no signs and symptoms of DKA or HHS, we decided to use degludec as BOT, expecting the effect to last much longer as basal insulin until the next HD session (48 or 72 h later).

Although the pharmacokinetic properties of the insulin analog degludec seem to be preserved independently of renal function [14], we took best care to avoid hypoglycemia because this patient could not perform SMBG because of decreased cognitive function and disabled fingers. The result of CGM suggested that asymptomatic hypoglycemia might have hardly occurred. In this case, why did this modified BOT work with a low dose of degludec, 24 units per week at a maximum? We suspected that the intensified OHA might have contributed greatly to the improvement of postprandial hyperglycemia as the glucose toxicity resolved. In fact, the patient's ability to secrete insulin seemed to be preserved as the postprandial C-peptide level was 4.6 ng/ml (1.5 nmol/l), which was not low even for the impaired C-peptide clearance in ESRD. However, degludec also might have contributed to the improved glycemic control, considering that the deteriorating glycemic control 9 months after starting BOT improved with an increased dose of degludec.

According to the pharmaceutical reference documents in Japan, vildagliptin 100 mg may be an overdose for diabetic hemodialysis patients, although there are some reports that it is not necessary to reduce the dosage of vildagliptin for this group. If the patient's glycemic control remains to be stable, we plan to reduce the dosage in the near future.

Good glycemic control has been reported to prevent the progression of diabetic complications and improve the prognosis [19–22]. In addition, a report shows that improvement of glycemic control is associated with a lower risk of mortality in HD patients with diabetes who have no preexisting CVD [10]. Based on this information, three-times-a-week degludec injection after HD can be considered an alternative therapy in patients who cannot inject insulin once a day by themselves, but who can take medicine and whose ability to secrete insulin has been preserved to achieve good and safe glycemic control. This regimen may be applicable to elderly patients who receive home-visit nursing care services.

In summary, this modified BOT with three-times-a-week degludec injection by medical staff may be useful for patients who cannot inject insulin by themselves. It may play a role for patients with diabetes for whom a standard basal insulin regimen is not available.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by any of the authors.

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