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STUDY OF REAL LIFE SAFETY AND EFFICACY OF INSULIN GLARGINE IN T2DM PATIENTS WITH ESTABLISHED CHRONIC KIDNEY DISEASE

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Background

- Diabetic kidney disease (DKD) is a common complication of Type 2 Diabetes (T2DM) and if not properly managed can rapidly progress to end stage renal disease (ESRD).[1]
- There is paucity of data on usage of insulin glargine in subjects with diabetes and chronic kidney disease (CKD) owing to lack of pharmacokinetic-pharmacodynamics studies in patients with varying magnitude of renal insufficiency.[2]

Aim

- To assess the safety and efficacy of insulin glargine in T2DM patients with established CKD (stage 3 and beyond).

Methodology

- Dual-centered, retrospective, real world observational study from the hospital registry for patients attending the outpatient department of endocrinology and/or nephrology.
- All patients were taking insulin glargine for a period of at least 24 weeks.

Inclusion Criterion

- Non-pregnant adult T2DM diagnosed as per ADA criterion (HbA1c>6.5%).
- Participants with CKD stage 3, 4 or 5.
- Participants receiving Glargine once a day.

Exclusion Criterion

- Patients with
  - *Diabetes type 1*
  - *Pregnant type 2 Diabetes*
  - *Patients with h/o hospitalisation during the period of observation*

Materials and Methods

- Demographic records with respect to age, gender, height, body weight, body mass index (BMI), blood pressure (BP) and duration of diabetes were collected from OPD database.
- Blood samples were investigated for
  - glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), post prandial plasma glucose (PPPG), blood urea nitrogen (BUN), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), urine albumin creatinine ratio (UACR), sodium (Na), potassium (K), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C).
- Subgroup analyses were done to see events of hypoglycemia in different stages of CKD.
- Data of only those patients were considered for final evaluation having both baseline and post-treatment values of the study parameters.

Results- Baseline Characteristics

- A total of 71 patients (46 male and 25 female) with CKD stage 3 & CKD stage 4 (mean GFR 40.17 ± 9.13 ml/min) were included in the study.
- The mean age of the patients and the mean duration of disease were 62.3 ± 1.34 and 15.98 ± 0.96 years, respectively.
- Baseline characteristics enlisted in Table 1

Table 1 - Baseline Characteristics

Male, n (%)	44 (61.97)
Female, n (%)	27 (38.03)
CKD Stage 3, n (%)	60 (84.51)
CKD Stage 4, n (%)	11 (15.49)
Age (years), Mean ± SEM	62.31 ± 1.34
Duration of Diabetes (years), Mean ± SEM	15.98 ± 0.96
Body weight (Kg), Mean ± SEM	70.41 ± 1.38
Body Mass Index (kg/m2), Mean ± SEM	27.13 ± 0.54
SBP (mm Hg), Mean ± SEM	148.7 ± 2.73
DBP (mm Hg), Mean ± SEM	81.3 ± 1.03
FPG (mg/dl), Mean ± SEM	183.44 ± 9.23
PPPG (mg/dl), Mean ± SEM	254.35 ± 10.41
HbA1c (%), Mean ± SEM	8.74 ± 0.25
Urine ACR, Mean ± SEM	594.12 ± 101.94
Serum Creatinine (mg/dl), Mean ± SEM	1.78 ± 0.05
eGFR (mL/min/1.73 m2), Mean ± SEM	39.65 ± 1.13
Serum Sodium, mEq/L	135.44 ± 0.83
Serum Potassium, mEq/L	4.44 ± 0.07
Total Cholesterol (mg/dl), Mean ± SEM	156.86 ± 3.88
High density lipoprotein (mg/dl), Mean ± SEM	44.92 ± 1.72
Triglycerides (mg/dl), Mean ± SEM	155.69 ± 6..96
Low density lipoprotein (mg/dl), Mean ± SEM	83.43 ± 3.41

Results

- At the end of 24 weeks study period, significant reductions were observed for FPG, PPPG and HbA1c, p<0.001 for all parameters. (Table 2)

Table 2: Changes in glycaemic study parameters values in 71 subjects with renal dysfunction

Glycemic Parameters	Baseline	Follow-up (24 weeks)	t value	p value (two-tailed)
	Mean ± SEM	Mean ± SEM		
FPG, mg/dL	183.44 ± 9.23	**118.59 ± 4.02**	7.12	<0.001
PPPG, mg/dL	254.35 ± 10.41	192.74 ± 5.87	5.36	<0.001
HbA1c, %	8.74 ± 0.25	7.72 ± 0.14	6.24	<0.001
p <0.05 considered as statistically significant, p computed by paired t-test				

Results (Contd..)

- A non-significant but modest increase in eGFR levels of 8 mL/min/1.73 m^2 (p=0.076) was demonstrated. (Table 3)
- A significant mean reduction of 305 mg/g in the urine ACR levels, p=0.006 was also achieved. (Table 3)
- However no significant changes were observed in BUN, Scr, sodium and potassium levels. (Table 3)

Table 3: Changes in renal function study parameters values in 71 subjects with renal dysfunction

Renal Function Tests	Baseline	Follow-up (24 weeks)	t value	p value (two-tailed)
	Mean ± SEM	Mean ± SEM		
Urine ACR, mg/g	594.12 ± 101.94	289.21 ± 62.04	2.89	0.006
Blood Urea Nitrogen, mg/dL	62.54 ± 4.49	58.83 ± 4.10	1.258	0.215
Serum Creatinine, mg/dL	1.78 ± 0.05	1.79 ± 0.07	-0.142	0.888
eGFR, (mL/min/1.73 m^2)	39.65 ± 1.13	41.11 ± 1.28	-1.799	0.076
Serum Sodium, mEq/L	135.44 ± 0.83	136.68 ± 0.86	-1.793	0.11
Serum Potassium, mEq/L	4.44 ± 0.07	4.42 ± 0.02	-0.032	0.975
p <0.05 considered as statistically significant, p computed by paired t-test				

- No significant changes were noted in any of the anthropometric parameters namely body weight, BMI, SBP, DBP (Table 4) or in the lipid parameters (LDL-C, TG, TC) except HDL-C level, which was found to be significantly decreased at the end of study period (Table 5).

Table 4: Changes in anthropometric study parameters values in 71 subjects with renal dysfunction

Anthropometric Parameters	Baseline	Follow-up (24 weeks)	t value	p value (two-tailed)
	Mean ± SEM	Mean ± SEM		
Body Weight, kg	70.41 ± 1.38	70.04 ± 1.3	1.12	0.269
BMI, kg/m^2	27.13 ± 0.54	26.99 ± 0.51	1.136	0.26
SBP, mmHg	148.7 ± 2.73	146.05 ± 1.75	1.27	0.209
DBP, mmHg	81.3 ± 1.03	81.5 ± 0.93	-0.20	0.84
p <0.05 considered as statistically significant, p computed by paired t-test				

Table 5: Changes in lipid study parameters values in 71 subjects with renal dysfunction

Lipid Parameters	Baseline	Follow-up (24 weeks)	t value	p value (two-tailed)
	Mean ± SEM	Mean ± SEM		
Total Cholesterol (mg/dl)	156.86 ± 3.88	148.04 ± 4.01	1.754	0.086
High density lipoprotein Cholesterol (mg/dl)	44.92 ± 1.72	40.63 ± 1.32	1.657	**0.009**
Triglycerides (mg/dl)	155.69 ± 6..96	144.02 ± 7.21	2.714	0.077
Low density lipoprotein Cholesterol (mg/dl)	83.43 ± 3.41	76.65 ± 2.78	1.197	0.26
p <0.05 considered as statistically significant, p computed by paired t-test				

Results- Hypoglycemia : Table 6

- The rate of hypoglycemia (set at <70 mg/dl) was found as 0.19 events per patient year in the overall study sample.
- Asymptomatic hypoglycemia (1.27 events versus 0.20 events per patient year, p<0.001), mild hypoglycemia (0.91 events versus 0.27 events per patient year, p=0.020) and severe hypoglycemia (0.55 events versus 0.10 events per patient year, p=0.013), was found to be higher in stage 4 CKD than stage 3 CKD but not nocturnal hypoglycemia (0.26 events versus 0.14 events per patient year, p=0.236).

Hypoglycemia Episodes/Events	Number (%)
Asymptomatic Hypoglycemia	20 (28.17)
Mild Hypoglycemia	13 (18.31)
Severe Hypoglycemia	6 (8.45)
Nocturnal Hypoglycemia	6 (8.45)

Hypoglycemia Episodes/Events	Number (%)	CKD Stage 4, N=11 Number (%) Event per patient year	p	Risk Ratio, 95% CI
Asymptomatic Hypoglycemia	13 (21.67) 0.20	7 (63.6) 1.27	**<0.001**	15.46, 3.48-68.63
Mild Hypoglycemia	9 (15) 0.27	4 (36.36) 0.91	**0.020**	5.31, 1.31-21.57
Severe Hypoglycemia	3 (5) 0.10	3 (27.27) 0.55	**0.013**	7.01, 1.2-40.83
Nocturnal Hypoglycemia	4 (6.67) 0.14	2 (18.18) 0.26	0.236	3.05, 0.486-19.19

Discussion

- Clinical efficacy and safety profile of insulin analogues are not clearly defined in patients with moderate renal failure and most of the reported studies are case reports[3] or consist small series of diabetic patients on dialysis.[4,5,6]
- Pscherer et al. reported the results of their study performed on 20 diabetic (4 type 1 and 16 type 2) patients with end stage renal disease on hemodialysis treated with insulin glargine.[7] In this nine-month study, HbA1c was reduced 0.9% ($p < 0.01$), severe hypoglycemic events were not reported and dry weight increased approximately 1.5 kg.
- Overall, our study results are in the same line as those of Nafiar et al.[8]
- In clinical trials, a single daily injection of insulin glargine provides glycemic control equivalent to that afforded by NPH insulin , but with a lower risk of hypoglycemia.
- The mean duration of diabetes in present study is 16 years which connotes an insulinopenic state similar to T1DM.
- FPG, PPPG & HbA1c values were found to be significantly reduced with Glargine treatment in 24 wk follow-up in this study.
- Weight and BMI did not change during the study period although the duration of study was too short to conclusively comment.
- The rate of hypoglycemia (0.19 events per person year) was similar to that of the landmark DCCT trial in T1DM subjects without renal dysfunction (0.17 events per person year) and incidence of hypoglycemia is much lower than previous reports of hypoglycemia in T2DM patients with CKD (1.29 events per person year).
- In the present study, at the end of six month treatment periods with insulin glargine, we achieved significant reduction in HbA1c (1.02%) much better than that reported by Pscherer et al.[7]
- Our patients also demonstrated a better weight profile than reported by Pscherer et al.[7] at the end of study period but a few hypoglycemic episodes were reported.
- Furthermore, significant reduction in ACR was observed in our study which implies an additional benefit of lowering CVD risk in this subgroup of patients.
- The renal endpoint also appears favourable with non-significant increase in GFR.

Conclusion

- Insulin glargine improved HbA1c in this short-term study and proved to be safe and well tolerated in patients with type 2 diabetes and diabetic kidney disease (Stage 3 and beyond).

References

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