GLA-100 Versus GLA -300 as Add on Basal Insulin in Basal Supported Oral Therapy – Real World Evidence from Eastern India

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ABSTRACT

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Materials and Methods: Anthropometric data, blood pressure, glycaemic parameters, creatinine, and insulin dosage at baseline and after a treatment period of 12 weeks were taken up for analysis retrospectively.

Results: Fasting, postprandial and HbA1C values were reduced significantly for both 54 patients in GLA-300 arm and 50 patients in GLA-100 arm. No change observed in anthropometric parameters, blood pressure and creatinine values between the two arms. Incremental dose of +5.41±0.69 units for GLA-300 cohort was required in contrast to 10.66±1.04 units for GLA 100 cohort. There were 6 episodes of hypoglycaemia in the GLA-300 cohort and 11 in the GLA-100 cohort.

Conclusion: GLA-300 appears to be a safer compared to GLA 100 as effective basal insulin.

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I. INTRODUCTION

Type 2 Diabetes Mellitus (T2D) is a disorder whose pathophysiology has evolved from the lack of insulin to the concept of ominous octet (1). Whether it be beta cell apoptosis (2) or dedifferentiation of beta cells to alfa cells (3) - the fact remains that the beta cell function in T2D subjects decline with time (4). During progression in the continuum of the disease there is oral antidiabetic drug (OAD) failure (5) – meaning only oral agents against diabetes at that point of time are unable to maintain the glycaemic targets.

Recently the concept of basal supported oral therapy (BOT) has gained strong grounds (6) wherein along with other permissible OADs, a basal insulin is initiated and titrated to achieve glycaemic target and to maintain it. The simple regimens available for basal insulin initiation and titration have paved the path for early insulin initiation.BOT, since its inception, used GLA-100 (Glargine U100) as the basal insulin, accepting the fact that the U100 version of Glargine was not an ideal basal insulin because of a small peak in between 6-8 hrs of its time action profile. (7). In early 2018, GLA-300 (Glargine U 300) was introduced in India with a better demonstrated PK /PD profile leading to ideal 24-hour coverage and a peakless time action profile (8) - thereby putting the "gold standard basal insulin "label attached to GLA-100 under the scanner. With availability of GLA-300, it's use as basal insulin in

BOT patients began to increase. Here, we retrospectively looked at the electronic medical records (EMR) to tease out data of patients on BOT receiving GLA-100 or GLA-300 for at least 12 weeks, to compare their efficacy and safety .

II. MATERIALS AND METHODS

This is a retrospective real-world registry based observational study carried out at the Endocrinology outpatient department of a tertiary care hospital of India between 1st June 2018 and March 31st, 2019. Insulin naive subjects on OAD who presented with osmotic symptoms and /or conformed to the Insulin initiation criteria of the Indian Insulin Initiation Guidelines (11) and were initiated on GLA-100 or GLA-300 (according to patients' choice due to price variability) at the Endocrine department were taken up for analysis.

2.1 Inclusion criteria

1. Insulin naive subjects on OAD who were on GLA100 or GLA 300
2. Patients who were followed up for at least 12 weeks
3. Patients who followed the titration algorithm provided by the Department as per glucometry values and maintained the complete dataset.
4. Patients whose age was between 18-70 years.

2.2 Exclusion criteria

1. Patients who required rescue prandial insulin
2. Patients with ill maintained dataset
3. Patients who dropped out of insulin therapy before completion of 12 weeks
4. Age below 18 years or greater than 70 years
5. Pregnant, intending to be pregnant or lactating mothers
6. Patients who were hospitalised during this 12-week study period

All patients who were initiated on Insulin were counselled to check fasting plasma glucose (FPG) weekly and empowered to titrate the insulin dosage according to a prespecified titration algorithm with telephonic assistance from departmental staff. The patients were recalled on week 2, week 4, week 8 and week 12 for dose titration as per the standard operating procedure (SOP) of the department. Patients receiving GLA 300 were started on an initial dose of 0.3 units/kg body weight as per the latest AACE guidelines (9) whereas GLA 100 was started at an initial dose of 10-14 units according to body weight as per existing SOP of the Department. Anthropometric data, blood pressure, glycaemic parameters, creatinine, and insulin dosage at baseline and after a treatment period of 12 weeks were taken up for analysis.

III. STATISTICAL METHODS

Descriptive and inferential statistics had been carried out in the present study. The measurements on the continuous scale were expressed as mean ± SD whereas the qualitative parameters were expressed as number and percentages. The baseline characteristics between the two arms were compared either by chi-square test or unpaired t-test. The changes in the study parameters from baseline to follow-up were assessed by paired t-test. Significance was assessed at a level of 5%. All data extracted were analysed using the Statistical Package for Social Sciences (SPSS) software version 21.0 (IBM Corp., North Castle, NY, USA).

IV. RESULTS

A total of 50 patients using GLA100 and 54 patients using GLA 300 were available after accounting for the inclusion and exclusion criteria. and their baseline characteristics are described in table 1.

Table 1: Baseline Characteristics

	I-Glar U-100 Cohort, N=50	I-Glar U-300, N=54	p - value
Male, n (%)	23 (46)	29 (53.70)	0.432*
Female, n (%)	27 (54)	25 (46.30)	
Age(years), Mean ± SEM	56.56 ± 1.57	57 ± 1.01	0.972
Body weight (Kg), Mean ± SEM	69.65 ± 2.13	68.74 ± 1.85	0.894
SBP (mmHg), Mean ± SEM	132.22 ± 2.21	128.61 ± 1.64	0.261
DBP (mmHg), Mean ± SEM	80.56 ± 1.31	80.5± 1.26	0.943
BMI (kg/m2), Mean ± SEM	26.18 ± 0.73	29.14 ± 2.71	<0.001
FPG (mg/dL), Mean ± SEM	230.69 ± 7.49	206 ± 13.1	0.194
PPG (mg/dL), Mean ± SEM	295.18 ± 11.75	278.7 ± 19.19	0.452
HbA1c (%), Mean ± SEM	9.61 ± 0.22	9.12 ± 0.26	0.165
Insulin Dose (IU), Mean ± SEM	13.44 ± 0.41	22.85 ± 2.29	0.001
Serum Creatinine (mg/dL), Mean ± SEM	0.95 ± 0.03	0.90 ± 0.04	0.876

Age ,body weight, blood pressure and glycaemic parameters were similar between the GLA 100 and GLA 300 subgroups at the baseline

Table 2: Change in study parameters at the end of follow-up period

	I-Glar U-100 Cohort, N=50			I-Glar U-100 Cohort, N=54		
	Baseline, Mean ± SEM	Follow-up Mean ± SEM	p Value	Baseline, Mean ± SEM	Follow-up Mean ± SEM	p Value
Body weight (kg)	69.65 ± 2.13	69.58 ± 2.13	0.71	68.74 ± 1.85	69.5 ± 1.91	0.649
BMI (kg/m^2)	26.18 ± 0.73	25.97 ± 0.69	0.63	29.14 ± 2.71	29.39 ± 2.72	0.758
SBP (mmHg)	132.22 ± 2.21	127.6 ± 1.59	0.046	128.61 ± 1.64	126.9 ± 1.55	0.287
DBP (mmHg)	80.56 ± 1.31	80.26 ± 1.27	0.921	80.5± 1.26	79 ± 0.80	0.327
FPG (mg/dL)	230.69 ± 7.49	154.78 ± 7.59	<0.001	206 ± 13.1	152 ± 9.44	<0.001
PPG(mg/dL)	295.18 ± 11.75	236.37 ± 10.58	<0.001	278.7 ± 19.19	224 ± 14.8	<0.001
HbA_{1c} (%)	9.61 ± 0.22	8.56 ± 0.18	<0.001	9.12 ± 0.26	8.34 ± 0.22	<0.001
Serum Creatinine, (mg/dL)	0.95 ± 0.03	0.99 ± 0.03	0.901	0.90 ± 0.04	0.89 ± 0.04	0.632
Insulin Dose (IU)	13.44 ± 0.41	24.1 ± 1.45	<0.001	20.2 ± 1.72	25.61 ± 2.41	0.582

Table 3

	GLA 100	GLA 300	p - Value
Percent Change in Body weight, Mean ± SEM	- 0.09 ± 0.02	1.10 ± 0.84	0.207
Percent Change in BMI, Mean ± SEM	- 0.72 ± 0.20	0.85 ± 0.54	0.361
Percent Change in SBP, Mean ± SEM	- 3.49 ± 2.98	- 1.32 ± 3.69	0.857
Percent Change in DBP, Mean ± SEM	- 0.37 ± 1.21	- 1.79 ± 0.91	0.133
Percent Change in FPG, Mean ± SEM	- 32.90 ± 12.23	- 26.72 ± 8.44	0.042
Percent Change in PPG, Mean ± SEM	- 19.29 ± 3.89	- 19.71 ± 3.93	0.802
Percent Change in HbA_{1C}, Mean ± SEM	- 10.76 ± 2.22	- 8.55 ± 2.11	0.069

p< 0.05 considered as statistically significant, p computed by unpaired t-test

There was statistically significant improvement of all glycaemic parameters (FPG, PPPG, HbA1C) in both the GLA 100 and GLA 300 cohorts. GLA 100 cohort showed substantial increase in the basal insulin dose between baseline and at 12-week. Percentage change in FPG was more in GLA 100 cohort than in GLA 300 arm and this change attained statistical significance (table 3)

Hypoglycaemia data was retrieved from the SMBG records and the updated EMR of the department. There were 6 episodes of hypoglycaemia in the GLA 300 cohort whereas the GLA 100 arm reported 11 episodes. This numbers though appeared numerically different, did not achieve statistical significance (p= 0.215). Severe and nocturnal hypoglycemia was greater in the GLA100 arm than in the GLA 300 arm. Details of hypoglycaemia episodes recorded are enumerated in table 4.

Table 4: Hypoglycemia Profile

	GLA - 300	GLA - 100	p - Value
Overall hypoglycemia, no. of event	6	11	0.215
Severe hypoglycemia, no. of event	1	4	
Nocturnal hypoglycemia, no. of event	0	2	
Event rate, per patient year	0.48	0.95	

V. DISCUSSION

When we compared the GLA300 and GLA100 arm for glycaemic efficacy we saw that GLA100 reduced FPG by 75.90+/-0.90 mg/ dl whereas GLA 300 reduced FPG by 54+/-3.66 mg/dl and both reductions were statistically significant (p< 0.001).However when we looked at the percentage reduction of FPG in both arm (table 3) there existed a difference, where GLA 100 arm experienced a reduction of FPG greater than that in the GLA 300 arm which was statistically significant. (p=0.042).This greater reduction of FPG by GLA 100 can be attributed to its pK / pD profile whereby it had a peak in the morning time (being administered during late evening hours and having a peak in between 6-8 hours) whereas GLA 300 having a flat time action curve lacked the peak and lagged behind in FPG reduction.

When we looked at PPPG, it was reduced by 58.81+/-1.17 mg /dl in the GLA 100 arm and by 54.7+/-4.39 mg/dl in the GLA 300 arm, both reductions were statistically significant (p<0.001). HbA1C reduction in the GLA100 arm was 1.05+/-0.04% whereas in the GLA 300 arm it was 0.78+/-0.04% and both changes were individually statistically significant (p<0.001). However when we looked at the percentage reductions in PPPG and HbA1C in the two arms and compared the two variables there was no statistically significant difference between the two arms (p=0.802 for PPPG and p=0.069 for HbA1C). There was a considerable numerical difference in the HbA1C reduction between the two arms which is a possible resultant of the greater FPG reduction in the GLA 100 arm.

GLA 100 arm underwent a statistically significant up titration (p<0.001), whereas there was insignificant up titration in the GLA 300 arm. The initial dose of GLA 100 was between 10-14 units as per existing SOP of the Department and hence required more up titration. On the other hand, GLA 300 being a new molecule, the initiation dose was 20-24 units as per the recent guidelines of AACE and thus required minimal up titration. Creatinine, body weight, BMI, systolic and diastolic pressure values in both the arms did not record statistically significant change either over 12 week follow up or when compared as

percentage reduction in these study variables. (table 2)

EDITION 3, an RCT which looked at insulin naive OAD failure subjects, (10) seemed to most appropriately match the cohort of patients included in this real world study (RWS). The mean age of patients in this RWS in the GLA100 arm was 56.56+/-1.57 years whereas in EDITION 3 it was 57.2 +/-10.3 years, the greater variability perhaps attributable to the much larger numbers (n=439) in EDITION 3. GLA 300 arm in our RWS had a mean age of 57+/-1.01 years whereas in EDITION 3 it was 58.2+/- 9.9 year. GLA 300 arm in the RWS had 53.70% males whereas in the RCT the percentage was 57.6, which are more or less comparable. However, in the GLA 100 arm, there was 46% males which was significantly lesser than the 57.2 % males reported in the GLA 100 arm in the RCT. A comparative table elucidating the differences in glycaemic parameters of the two arms in the RCT viz EDITION 3 versus our RWS is given in table5.

Table 5

	GLA – 100 RWS	GLA – 100 RCT	GLA – 300 RWS	GLA – 300 RCT
FPG Reduction	-75.90+/-0.90 mg/dl	68.4+/-1.98mg/dl	54.+/- 3.66mg/dl	61.38+/-1.8 mg/dl
HbA_{1C} Reduction	-1.05+/-0.04 %	-1.46+/- 0.05 %	0.78+/-0.04%	-1.42+/-0.05%

The GLA 300 arm achieved a HbA1C reduction of -1.42 +/- (0.05)% at the 6-month mark in EDITION 3 whereas the reduction was -0.78 +/- (0.04) % at the 12 week mark in our RWS, a much lower figure which may be attributed to the difference in time period of the two studies. It may however be noted that the reduction of FPG was more with GLA 100 than with GLA 300 in both the RCT and our RWS.

There were 6 episodes of documented hypoglycaemia in the GLA-300 arm whereas there were 11 episodes of documented hypoglycaemia in the GLA-100 arm. (table 4) In the GLA 100 arm there were 4 episodes of severe hypoglycaemia requiring third party assistance, of which 2 were nocturnal. When anualised calculation was done, 0.95 events of hypoglycaemia/patient/year in the GLA-100 arm and 0.48 events of hypoglycaemia/patient/year in the GLA-300 arm was recorded in our RWS. The annualised event rate of hypoglycaemia was 6.8 events/patient/year in the GLA 300 arm and 8.5 events/patient/year for GLA 100 in EDITION 3. Hypoglycemia events are reported to be low during the initial titration phase of GLA-300 compared to GLA-100.[11] Even if we consider the annualized event rate of first 8 weeks titration phase data for GLA 300, the event rates were 4.5 events/patient/year in the RCT which is still higher than our RWS.

This significant difference in event rates of hypoglycaemia in both the GLA-100 and GLA-300 arm may be attributed to the shorter duration of our study period (only 12 weeks). Another contributing factor may be less aggressive monitoring in the RWS (weekly once and when symptomatic) in comparison to the conventional intensive monitoring in RCT (EDITION 3). Finally, failure to elucidate the non-documented mildly symptomatic and asymptomatic hypoglycaemia in both the arms may have also been an important contributor towards the low rates of hypoglycaemia obtained in our RWS.

Small sample size, short duration of study, minimal monitoing and failure to pickup the non documented asymptomatic hypoglycaemic episodes are the major limitations of our study. Studies with larger sample size with more frequent glucose monitoring are required to further validate the findings of this RWS.

VI. CONCLUSION

As basal insulin therapy in insulin naive OAD failure patients, GLA 300 is equally efficacious as GLA 100 in reduction of glycemic parameters. With regards to hypoglycaemia GLA300 has the superior safety profile. These real-world findings are in line with the evidence shown in the EDITION 3 RCT.

Conflict Of Interest :

NONE

Funding :

NONE

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