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Better Glycemic Outcomes with Less Insulin on Transition from Continuous Subcutaneous Insulin Infusion to Basal Insulin Combined with GLP1 Receptor Agonist and / or Metformin and Sulfonylurea

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Abstract

Background: Continuous subcutaneous Insulin infusion (CSII) therapy for management of subjects with type 2 diabetes is being promoted despite lack of adequate assessment of cost efficacy and safety in large clinical trials. Moreover, CSII for management of Type 2 diabetes is not approved by insurance plans in USA. Therefore, the impact of therapy with basal insulin Glargine, Sulfonylurea, Metformin and Glucagon-like Peptide-1 Receptor Agonist (GLP 1 RA) if needed on glycemic outcomes was examined in subjects with type 2 diabetes (T2DM) following withdrawal from CSII because of denial by insurance plans.

Subjects: 12 obese subjects 8 men and 4 women (BMI, 34-42 kg/m^2), ages 45-65 years with type 2 diabetes using CSII were referred to endocrinology clinic for further management during 2 year period, 1/1/16 - 12/31/17. The diagnosis of type 2 Diabetes was confirmed by presence of C-Peptide. The duration of diabetes was 5-12 years. Liver enzymes were <2 times normal and EGFR was >60 ml. Following withdrawal of CSII, treatment with Metformin 500 mg. PM after supper, Sulfonylurea Glipizide 20mg twice daily or Glimepiride 8 mg. daily AM based on availability on insurance formulary and SC basal insulin Glargine, 0.2 units/kg in AM was initiated. Metformin was gradually increased at weekly interval to 1000 mg twice daily and insulin Glargine was increased by 2 units every 3 days until AM blood sugar ≤ 6.6 mM/L was attained. Fasting plasma glucose, HbA1c, daily insulin dose, body weight and hypoglycemic events were determined prior to withdrawal of CSII and at 6 months after changing treatment regimen. At this time, in subjects with HbA1c >7%, GLP1 RA approved by insurance, e.g. Exenatide or Liraglutide sc. was initiated and titrated to maximum daily doses. Glycemic outcomes were re-evaluated at 12 months. Comparisons were conducted between two regimens for glycemic outcomes and recurring costs.

Results: In 7 subjects, HbA1c and fasting plasma glucose were 7.6%-8.2% and 8.2-9.2 mM/L prior to discontinuation of CSII and declined to ≤ 7.0% and ≤ 6.8 mM/L respectively at 6 months with changed regimen. Hypoglycemic events declined from 4 - 7 during the last 4 weeks of CSII to 0 -2 during the 6th month of the changed regimen.

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The glycemic outcomes remained unaltered at 12 months. In the remaining 5 subjects, HbA1c levels declined from 8.2%-9.0% prior to discontinuation of CSII to 7.5%-8.0 % despite attaining fasting plasma glucose ≤ 6.6 mM/ l. Hypoglycemic events decreased from 5 - 8 during last 4 weeks of CSII to 1 - 2 during the 6th month of changed regimen. On addition of GLP 1 RA, HbA1c and hypoglycemic events declined further at 12 months to ≤ 6.8% and 0-2 respectively while maintaining fasting plasma glucose ≤ 6.6 mM/ l. Total average daily insulin dose of 120 ± 22 units with CSII declined to 55 ± 8 units at 12 months with changed regimens. Finally, the daily costs were significantly lower with combination therapy as compared with CSII.

Conclusion: Sustained desirable glycemic outcomes including markedly reduced hypoglycemic events are attainable with lower costs with basal insulin Glargine and non-insulin drugs e.g. SU, Metformin, GLP 1 RA on withdrawal of CSII in subjects with type 2 diabetes.

1. Introduction

Global population of subjects with Diabetes aged 20-79 years was estimated to be 450 million in 2015 and is predicted to rise to 642 million by 2040 [1]. Beta cell function is thought to gradually decline with increasing duration of the disease although several studies have established that progressive beta cell failure is neither total nor universal [2-4]. Therefore, many subjects with type 2 diabetes (T2DM) require insulin therapy in the long term. However, some of these subjects fail to attain desirable glycemic control despite administration of a combination therapy consisting of basal Insulin with multiple mealtime rapid acting insulin injections in a high daily insulin dose (>1.5 units/kg). Several studies have documented improvement in glycemic control in these subjects on implementation of continuous subcutaneous insulin infusion (CSII) also labeled 'insulin pump' therapy [5-9]. However, most insurance plans in USA deny approval for CSII in subjects with type 2 Diabetes especially with detectable endogenous insulin secretion documented by presence of c-peptide in circulation. Moreover, review of English literature yielded no data regarding reinitiation of non-insulin agents in combination with basal insulin in management of subjects with type 2 diabetes. Therefore, we assessed efficacy of therapy using oral agents in combination with basal insulin Glargine with further addition of GLP1 RA if required in subjects with type 2 diabetes following discontinuation of CSII therapy because of denial by the insurance plans.

2. Subjects and Methods

Data was collected retrospectively by examining the records of 12 obese subjects, 9 men and 3 women with type 2 diabetes who were referred to the endocrinology clinic during period of 2 years between January 2016 and December 2017 for further management because of withdrawal of CSII therapy due to denial by their insurance formularies despite preauthorization and appeal. The study protocol was approved by Institutional Review Board at the medical center. The major inclusion criterion was presence of serum c-peptide level >1.0 ng/dl confirming the diagnosis of type 2 DM (T2DM). The duration of type 2 DM ranged between 5 to12 years. The other inclusion criteria were obesity with BMI >30 kg/m2, HbA1c >7.0% and fasting plasma glucose >7 mM/L. The exclusion criteria were patients with undetectable serum c-peptide concentration, well established diagnosis of type 1 DM, EGFR <60 ml, serum creatinine levels >1.5 mg/dL and liver enzymes >2.5 times upper normal limit. Following withdrawal of CSII, treatment with Metformin 500 mg (PM), Glimepiride 8 mg AM and SC basal insulin Glargine, 0.2 units / kg BW in AM was initiated. Metformin was gradually increased at weekly interval to 1000 mg

twice daily and insulin Glargine was increased by 2 units every 3 days until AM blood sugar <6.6 mM/L was attained as recommended by American Diabetes Association (ADA) Guidelines [11].

Fasting plasma glucose, HbA1c, liver enzymes, serum urea nitrogen, creatinine and electrolytes were determined prior to withdrawal of CSII and at 6 months after changing treatment regimen. At this time, in subjects with HbA1c >7%, GLP1 RA approved by insurance plan of individual subject, e.g. SC Exenatide 5 mg twice daily before meals or Liraglutide 0.6 mg SC. once daily before breakfast was initiated and titrated to maximum daily dose after 4 weeks as recommended; 10 mg twice daily for Exenatide and 1.8 mg once daily for Liraglutide. Laboratory tests were revaluated at 12 months.

Comparisons were conducted between two regimens for recurring costs for equipments, frequency of hypoglycemic episodes, fasting blood glucose monitoring and average daily requirement of insulin needed to attain desirable fasting blood glucose <7.0 mM/lL. Statistical analyses were conducted using student's 't' test and analysis of variance. All data are presented as mean+ standard error of mean (Mean ± SEM).

3. Results

Population comprised of 12 obese subjects, 9 men and 3 women with BMI 34-42 kg/m^2 and ages, 45-65 years. Diagnosis of type 2 Diabetes was established by documentation of desirable glycemic control while receiving oral agents for several years as well as fasting c-peptide concentration of >1 ng/dl. In 7 subjects, HbA1c levels were 7.6% -8.2% prior to discontinuation of CSII and declined to ≤ 7.0% at 6 months on transitioning to basal insulin Glargine and oral medications, Metformin and Glimepiride and remained unchanged by the end of the year (TABLE 1). A significant decline was also noted in fasting plasma glucose from 8.2-9.2 mM/L on CSII to ≤ 6.8 mM/L at 6 months and was maintained at 12 months after discontinuing CSII (TABLE 1). The frequency of hypoglycemic events during the last 4 weeks while on CSII was 4-7 and declined to 0-2 during the 6^{th} month of the changed regimen and stayed stable for that last 4 weeks at 12 months (TABLE 1). Finally, a daily insulin dose following transition from CSII declined markedly with a modest weight loss (TABLE 1).

TABLE 1. **Fasting plasma glucose (FPG), HbA1c, daily insulin dose (DID), body weight (BW) and number of hypoglycemic episodes (hypoG) during last 4 weeks of therapy prior to (pre Rx) and after (post Rx) switching from CSII to combination therapy with basal insulin glargine, metformin and Glipizide in 7 subjects with T2DM who attained A1c ≤ 7% at 6 months and 12 months.**

	Pre RX	**Post Rx 6 months**	**Post Rx 12 months**
FPG (mM/l)	8.7 ± 0.8	6.7 ± 0.1*	6.8 ± 0.2*
HbA1C (%)	7.9 ± 0.5	6.7 ± 0.3*	6.8 ± 0.3*
DID (units)	126 ± 22	62. ± 19*	60 ± 12*

BW(KG)	126 ± 21	121 ± 20	120 ± 22
HypoG	5.4 ± 1.6	1.8 ± 0.9*	2.0 ± 1.1*

In the remaining 5 subjects, HbA1c levels were 8.2%-9.0% prior to discontinuation of CSII therapy and declined to 7.5%-8.0% after changing the regimen to basal insulin Glargine and oral agents despite attaining fasting plasma glucose ≤ 6.6 mM/l (TABLE 2). The number of hypoglycemic events decreased from 5-8 during 4 weeks prior to CSII withdrawal to 1-2 during the 6th month of changed regimen (TABLE 2). On addition of GLP 1 RA to initial changed regimen of Metformin, Glimepiride and basal insulin Glargine, HbA1c and hypoglycemic events declined further at 12 months to ≤ 6.8 % and 0-2 while maintaining fasting plasma glucose <6.6mM/l respectively (TABLE 2).

Total average daily insulin dose of 120 ± 22 units while using CSII declined to 55 ± 8 units at 12 months with this regimen (TABLE 2). Body weights of these subjects declined significantly by 6 months with a further significant weight loss by 12 months. Finally, the daily costs were significantly lower because of lesser daily insulin dose with less hypoglycemic events and the lower costs incurred for oral agents, basal insulin Glargine and GLP 1 RA as well as the equipment required for switched therapy when compared with the total expenses incurred for CSII including home blood glucose monitoring [$p<0.05$].

TABLE 2. **Fasting plasma glucose (FPG), HbA1c, daily insulin dose (DID), body weight (BW) and number of hypoglycemic episodes (hypoG) during last 4 weeks of therapy prior to (pre Rx) and after (post Rx) switching from CSII after addition of Exenatide to combination therapy with basal insulin glargine, metformin and Glipizide at 12 months in 7 subjects with T2DM who failed to attain A1c ≤ 7% at 6 months.**

	Pre RX	**Post Rx 6 months**	**Post Rx 12 months**
FPG (mM/l)	8.8 ± 0.8	6.7. ± 0.4*	6.6. ± 0.3*
HbA1C (%)	8.6 ± 0.7	7.6 ± 0.4*	6.6 ± 0.3*
DID (units)	128 ± 25	61 ± 11*	52 ± 6*
BW(KG)	127 ± 21	123 ± 20	121 ± 17
HypoG	5.6 ± 1.7	1.6. ± 0.6*	1.4. ± 0.4*

4. Discussion

This study demonstrates that in subjects with type 2 diabetes, initiation of therapy consisting of Metformin, Glimepiride and basal insulin Glargine following withdrawal of CSII resulted in significant improvement in glycemic control (TABLE 1). This finding is consistent with previous data in the literature as demonstrated in several clinical trials [12-18]. Improvement in glycemic control in 7 subjects following treatment with combination therapy may be attributed to lowering of fasting hyperglycemia induced by reduction of overnight hepatic glucose production by basal insulin Glargine and lowering of postprandial hyperglycemia by rise in meal stimulated endogenous insulin secretion caused by Glimepiride as well as improvement in sensitivity of both exogenous and endogenous insulin by Metformin.

In the remaining 5 subjects, despite lowering of fasting plasma glucose to desirable goal, HbA1c failed to decline to $\leq$ 7%. Attainment of desirable HbA1c level on addition of Exenatide or Liraglutide indicates further improvement in post prandial hyperglycemia via stimulation of insulin secretion and inhibition of glucagon release, a well- established effect of GLP-1 receptor agonist [19-36]. Lack of significant change in body weights or modest weight loss on withdrawal of CSII and following administration of alternative regimens throughout the study period has been documented in previous studies using basal insulin Glargine in AM in combination with Metformin and SU with or without GLP-1 receptor agonist [36-40].

Finally, a significant decline in the frequency of hypoglycemic episodes occurring with combination therapy consisting of basal insulin Glargine and Glimepiride, Metformin, and GLP 1 receptor agonist than with those previously on CSII may be secondary to the decline in the daily insulin dose (TABLE 1 & 2).

We believe that improvement in glycemic outcomes and lowering hypoglycemic events, body weight and cost are responsible for increased compliance and better adherence by the patients to these regimens [36-43] . However, this study has several limitations including retrospective observational parallel design, lack of comparison with a control group administered placebo, comparative data with other hypoglycemic agents, and influence of concomitant disorders as well as drugs used for the management of the same. However, the findings of a better efficacy of attaining desirable glycemic goals and lower cost of the treatment may be are important in the light of difficulty in obtaining approval for CSII therapy by the insurance formularies of these subjects with T2DM.

The use of CSII among subjects with T2DM poses a few drawbacks as the technology behind CSII is quite intricate which may be difficult for most elderly subjects with T2DM because of their inability to adapt to new technology. Advanced age also makes it more difficult for these subjects to modify their lifestyle including diet and exercise [5-7]. Finally CSII is usually not approved by the insurance company for patients with T2DM because of inability to establish evidence of insulin deficiency, similar to subjects with Type 1 DM. Therefore, the brunt of the cost for usage of insulin pump falls directly on patients with T2DM and makes it unaffordable [10,43].

In final analysis, switching the treatment regimen from CSII to a combination therapy consisting of basal insulin Glargine, Metformin and Glimepiride in some and further addition of GLP-1 receptor agonist in other subjects with T2DM improved glycemic control with less hypoglycemia and decreased daily dose of insulin rendering it more convenient, compliant and cost effective.

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