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LOWER DAILY DOSE WITH BETTER OUTCOMES WITH ORAL AGENTS AND AM INSULIN TOUJEO ADMINISTRATION THAN LANTUS WHILE ATTAINING DESIRABLE GLYCEMIC CONTROL IN TYPE 2 DIABETES

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ABSTRACT

Background: Lower daily dose with better outcomes with oral agents and AM insulin Toujeo administration than Lantus while attaining desirable glycemic control in type 2 Diabetes: Clinical trials (Edition) documented higher daily dose of Toujeo (Insulin Glargine U 300) to achieve non inferior glycemic control compared to Lantus (Insulin Glargine U100). In these trials, both insulins were administered in late evening (PM) or bedtime (HS). We recently documented several therapeutic advantages of Lantus administration in AM as compared to HS. **Objective:** Comparison between glycemic and other outcomes following therapy with AM administration of insulin Toujeo vs. Lantus in subjects with type 2 Diabetes with lapse of desirable glycemic control while receiving oral agents. **Subjects and methods:** 16 consecutive adult subjects, with history of type 2 diabetes were recruited because of rise in HbA1c over 8% while receiving oral agents. Subjects were randomized to 2 groups: adjunctive therapy with Insulin Toujeo or Lantus, initial dose, 0.2 units/ kg to be administered in AM at same time daily. Both insulins were titrated by 2 units, every 4 and 3 days for Toujeo and Lantus respectively until AM preinjection blood sugar, 80-130 mg/dl was attained. Daily dose was further adjusted to maintain AM blood sugar in the same range. Subjects were requested to determine blood sugars to confirm hypoglycemia (blood sugar <70 mg/dl) on occurrence of symptoms and institute treatment. Subject also continued same diet and activity profile and medications for other disorders throughout the study period of 6 months. Fasting plasma glucose (FPG), HbA1c and body weight (BW) were determined prior to and again at 3 and 6 months. Daily dose of insulin at 6 months and number of hypoglycemic events (hypo g) during 6 months of treatment are reported. Statistical comparisons between groups are conducted by student's 't' test and analysis of variance. All data are reported as Mean ± SEM. **Results:** Mean ages and duration of diabetes were not significantly different between groups (Toujeo, 48 ± 4 and 13 ± 4 years; Lantus, 51 ± 4 and 11 ± 5 years). FPG and HbA1C declined to 80-130 mg/dl and < 7.5 % respectively. Daily insulin dose/ kg BW and number of hypoglycemic events were significantly lower in subjects administered insulin Toujeo as compared to subjects receiving Lantus. Moreover, daily dose of insulin Toujeo required to reduce HbA1c concentration by 1 point from initial level was also significantly lower when compared with insulin Lantus. Body weights were not significantly different at 6 months when compared to pretreatment with either insulin Toujeo or Lantus although the change in BW with Toujeo (-1.0 ± 0.3 kg) was significantly different when compared with Lantus (3.2 ± 0.7 kg; $p < 0.05$). No significant correlations were noted between daily insulin dose on one aspect and age, duration of diabetes, body weight and initial FPG or HbA1C on the other for either insulin. **Conclusion:** Desirable glycemic control can be attained by addition of either insulin Toujeo or Lantus to oral agents in subjects with type 2 Diabetes. However, when administered in AM, daily dose of insulin Toujeo may be lower with less hypoglycemic events and greater weight neutrality in comparison to insulin Lantus. Thus, insulin Toujeo may be more effective and safer than Lantus.

KEYWORDS: Lower daily dose with Toujeo effective and safer than Lantus.

INTRODUCTION

Insulin Toujeo (insulin glargine U 300) was recently added to the armamentarium of basal insulins for management of hyperglycemia in subjects with both type 1 and type 2 diabetes. Several clinical trials (Edition program) documented lower incidence of hypoglycemia and less weight gain with administration of insulin Toujeo in comparison to insulin Lantus (insulin glargine U 100) in subjects with type 2 diabetes.[1-10] However, the same trials reported that the daily dose of Insulin Toujeo was 10-15% greater than insulin Lantus while attaining similar glycemic control.[1-10] However, both insulins were administered exclusively in PM. Moreover, the data regarding the comparison between outcomes following

administration of both insulins in AM is lacking despite approval by regulatory agencies for use at any time of the day as long as the time remains the same every day. Therefore, we conducted a comparative study to examine the impact of daily AM administration of insulin Toujeo and insulin Lantus in subjects with type 2 diabetes with inadequate glycemic control while receiving the combination of the same oral agents, e. g. Metformin and Sulfonylurea Glimepiride or both these agents and Sitagliptin in the maximum tolerated daily dose.

Subjects and Methods

16 consecutive subjects, 9 men and 7 women with history of type 2 diabetes and ages, 34-70 years were recruited from Endocrinology clinic during 6 months between April 1 and September 30, 2016 after referral because of lapse of glycemic control with a rise in HbA1c over 8 % on 2 occasions at interval of 3 months while receiving 2 or 3 oral agents in their maximum tolerated daily doses; Metformin 2000 mg and Glimepiride 8 mg or both these agents and Sitagliptin 100 mg. Inclusion criteria were liver enzymes < 1.5 times the highest normal levels, absence of renal dysfunction documented by serum creatinine level indicating EGFR > 60 ml and other disorders, e.g. hypertension, atherosclerotic cardiovascular disease, dyslipidemia, neuropathy etc. being stable without requirement for a change in daily dose of drugs for 6 months prior to enrollment. Subjects hospitalized for any disorder within previous 6 months and subjects unable to provide informed consent were excluded. Pregnant women were excluded as well. Subjects were randomized to 2 groups: AM administration of Insulin Toujeo or Lantus, daily dose, 0.2 units/ kg. BW, with instruction to administer in AM same time daily throughout the study period. Both insulins were increased by 2 units, every 4 and 3 days for Toujeo and Lantus respectively until AM preinjection blood sugar, 80-130 mg/dl, determined by a finger stick using a glucometer (Freestyle Freedom Lyte, Abbott Pharma inc, Abbott Park, Illinois) as recommended by American Diabetes Association was attained.[11] Daily dose was further adjusted if needed to maintain AM blood sugar in the same range. Subjects were requested to determine blood sugars to confirm presence of hypoglycemia (blood sugar <70 mg/dl) as recommended by American Diabetes Association on occurrence of symptoms suggestive of hypoglycemia and institute treatment e.g. 2 glucose tablets 4 g each or 4 oz orange juice or regular soda such as Sprite or Coca-Cola.[12] They were also requested to recheck blood sugar after 20 minutes to confirm rise in blood sugar > 80 mg/dl with relief of symptoms. Finally, subjects and their next of kin or caregivers were instructed to administer the same form of sugar described earlier and contact emergency telephone number 911 if improvement in symptoms was not noted. Hypoglycemic events were classified according to guidelines by American Diabetes Association: 'mild or level 1 or alert ' (blood sugar< 70 mg/dl), ' level 2 or clinically significant' (blood sugar<54 mg/dl), both not requiring secondary attention and 'severe' defined as a change in state of consciousness or/ and requiring resuscitation with assistance by another person.[12] Subjects were also instructed to continue same diet and activity profile as well as medications for other disorders throughout the study period of 6 months. Fasting plasma glucose (FPG), HbA1c and body weight (BW) were determined prior to and at 3 and 6 months following addition of insulin. Daily dose of insulin required to attain fasting blood sugar, 80-130 mg/dl as well as number of hypoglycemic events during 6 months of treatment in both groups are reported. Statistical comparisons between groups are conducted by student's 't' test and analysis of variance. All data are reported as Mean ± Standard Error of Mean (SEM).

RESULTS

Mean age, duration of diabetes and gender distribution were not significantly different between groups (age, Table1). 6 subjects in both groups were receiving Metformin 2000 mg and Glimepiride 8 mg daily while 2 subjects in each group was treated with Sitagliptin 100 mg in addition to Metformin and Glimepiride in the same daily doses. Fasting plasma glucose declined significantly by 3 months in all subjects and attained desirable levels of 80-130 mg/dl by 6 months with mean concentrations being not significantly different between subjects in both groups (Figure 1 and Table 2). HbA1C concentrations declined significantly by 3 months in all subjects in both groups as well reaching levels below 7.5% at 6 months with mean values being not significantly different amongst groups (Figure 2 and Table 2). However, HbA1c concentration < 7% was attained at 6 months in 6 of 8 subjects treated with insulin Toujeo and 7 of 8 subjects administered insulin Lantus.

Total daily insulin dose at the end of the study period was 55 ± 6 units with a range of 16 - 87 units (0.15 - 0.92 units/ kg BW) in subjects administered Toujeo and was therefore not significantly different when compared to 54± 7 units with a range of 19 - 93 units (0.18 -1.0 units / kg BW) in subjects treated with Lantus. However, mean daily dose of insulin expressed as units/ Kg. BW was significantly lower for insulin Toujeo when compared to insulin Lantus (Table 3). Moreover, the average daily insulin doses at 6 months required in 2 subjects in each group receiving all 3 drugs; (Toujeo, 0.23 units and Lantus, 0.27 units / kg BW) were about 50% lower than subjects using metformin and glimepiride with a significant difference ($p<0.05$) between groups. Finally, the daily dose of insulin Toujeo required to reduce HbA1c concentration by 1 point from initial level was also significantly lower when compared with insulin Lantus (Table 3). However, no significant correlations were noted between daily insulin dose on one aspect and age, duration of diabetes, body weight and initial FPG or HbA1C on the other in either of the groups or all subjects.

Body weight was not significantly altered when comparisons were conducted between body weights prior to initiation and at the end of study period in subjects receiv-

ing either insulin Toujeo or Lantus (Table 2). However, the change in body weight following treatment with insulin Toujeo (-1.0 ± 0.3 kg) from baseline was significantly different ($p < 0.05$) as compared to that noted in subjects receiving Lantus (3.2 ± 0.7 kg). Finally, number of hypoglycemic events were significantly lower in subjects administered insulin Toujeo as compared to subjects receiving Lantus (Table 3). However, all hypoglycemic events were 'mild' with none being nocturnal or of 'severe' variety.

Table 1: Demographic Charecteristics in Study Participants Divided into 2 Groups According to Insulin.

Insulin	Sex (M/ F)	Age (Years)	Duration of Diabetes (Years)
Toujeo.	5/3	48 ± 4	13 ± 4
Lantus.	4/4	51 ± 4	11 ± 5

Table 2: Fasting plasma glucose (FPG), HbA1C and Body Weight (BW) prior to (Pre Rx) and at 6 months following treatment (Post Rx) with Insulin Toujeo or Insulin Lantus as well as Daily Insulin Dose at 6 months and Number of Hypoglycemic Events (Hypo G) during 6 months.

Insulin	Pre Rx FPG	Post Rx FPG 3 Month	Post Rx FPG 6 Month	Pre Rx HbA1C	Post Rx HbA1C 3 Month	Post Rx HbA1C 6 Month
Toujeo	261±18	128±11✻	109±6✻	9.8±0.5	6.7±0.2✻	6.7±0.2✻
Lantus	237±15	128±9✻	113±6✻	8.6±0.4	7.1±0.3✻	6.6±0.2✻

✻ $p < 0.001$ vs. Pre Rx

Table 3: Body Weight (BW) prior to (Pre Rx) and at 6 months following treatment (Post Rx) with Insulin Toujeo or Insulin Lantus as well as Daily Insulin Dose at 6 months and Number of Hypoglycemic Events (Hypo G) during 6 months.

Insulin	Pre Rx BW	Post Rx BW	Daily Insulin Dose/kg	Hypo G/subject
Toujeo	128±9	127±10	0.45±0.06✻	1.1±0.3†
Lantus	106±6	109±6	0.51±0.08	3.6±1.2

✻ $p < 0.05$ vs. Lantus; † $p < 0.01$ vs. Lantus

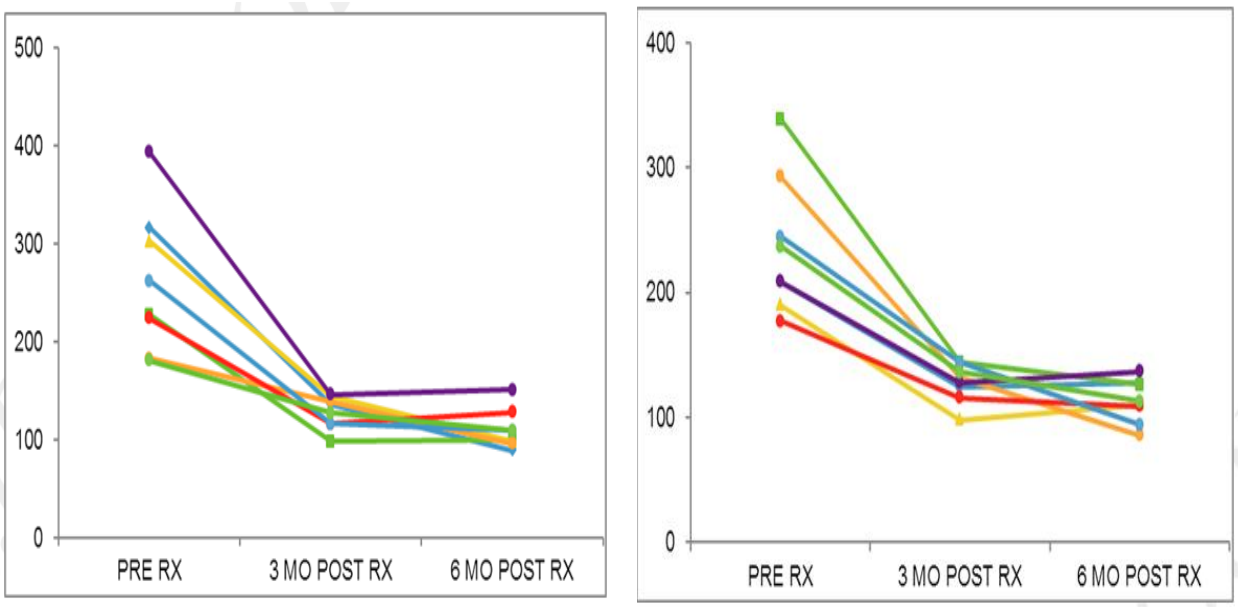

Figure 1: Fasting plasma glucose levels in subjects prior to (PRE) and months (MO) after (POST) treatment (RX) with insulin Toujeo (upper panel) and insulin Lantus (lower panel).

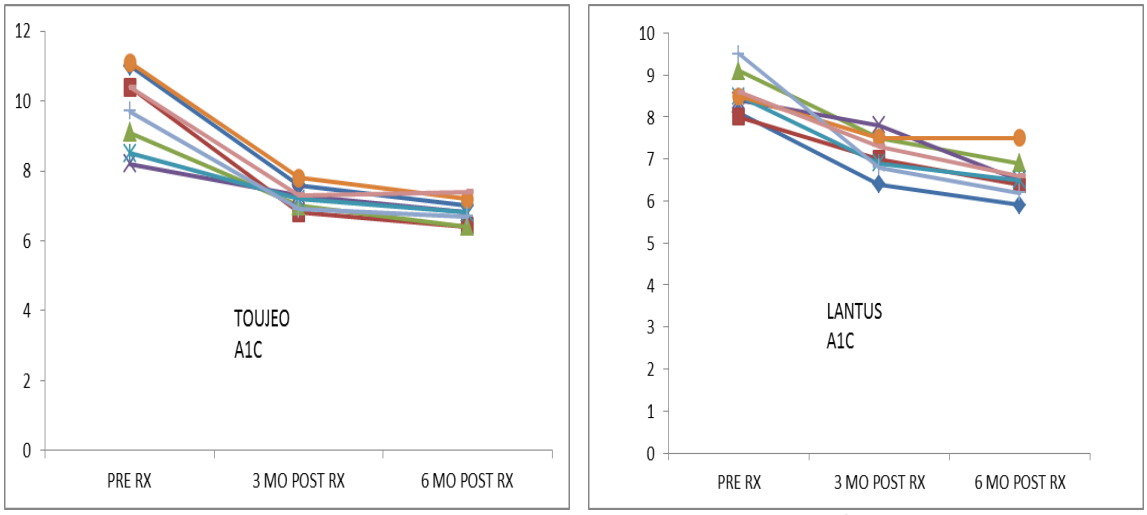

Figure 2: HbA1c concentrations in subjects prior to (PRE) and months (MO) after (POST) treatment (RX) with insulin Toujeo (upper panel) and insulin Lantus (lower panel).

DISCUSSION

We have previously demonstrated better glycemic control with less hypoglycemia with almost complete remission of nocturnal events and weight neutrality following administration of insulin Lantus in AM when compared with the same outcomes noted following administration of insulin Lantus at bedtime.[13] Similar advantages were noted in other studies with administration of insulin Lantus in AM over other alternative times of administration including the bedtime.[14-17] However, the daily dose was about 10% greater while insulin Lantus was administered in AM as opposed to bedtime.[13-17] Moreover, the major clinical 'Edition' trials in subjects with type 2 diabetes showed less hypoglycemia and the less weight gain with use of insulin Toujeo compared to insulin Lantus while attaining non inferior glycemic control.[1-10] However, the daily dose of insulin Toujeo in these 'Edition' clinical trials was about 10-15% greater than insulin Lantus.[1-10] This finding may be attributed to multiple factors: 1) lack of uniformity in terms of number of oral agents as evident in previous studies.[1-10]; 2] variability of the oral drugs as well as their daily doses used in combination[1-10]; 3] well established variability of insulin sensitivity in individual subjects despite similar body weights due to visceral obesity, sleep disturbances, depression, exercise, stress or disorders with increased circulating concentrations of counter regulatory hormones, I.e. Cortisol, catechoamines, glucagon and growth hormone(18-28) and 4) PM administration of both insulins especially in the light of evidence showing benefits of administration of insulin Lantus in AM over PM or bedtime.[13-17]

This study documents that both basal insulins, Toujeo and Lantus administered in AM are effective in attaining desirable glycemic goals recommended by American Diabetes Association, e.g. fasting plasma glucose 80 - 130 mg/dl ad HbA1C <7%[12] in majority of subjects with type 2 Diabetes after lapse of glycemic control while receiving combination therapy consisting of 2 or 3 oral agents, Metformin and SU Glimepiride or both and Sitagliptin in maximum tolerated daily doses. This finding is consistent with the efficacy data in 'Edition' trials in subjects with type 2 diabetes.[1-10] However, it is apparent that Insulin Toujeo may be more effective in comparison to Insulin Lantus as expressed by the lower daily dose, units/ kg BW to attain desirable HbA1c levels as well as the lesser requirement to lower HbA1C by one point from the pretreatment level. Furthermore, the daily dose for either basal Insulin required to attain desirable glycemic goal ranged widely, irrespective of the body weight, initial HbA1c level, duration of diabetes, the age of subjects etc. as documented in several previous reports.[29-51] Alternatively, the daily insulin dose may be influenced by the number of oral agents used in combination as evidenced by the lower daily dose with use of 3 drugs as compared to 2 drugs as well as their daily doses and the type of oral agents e.g. metformin, sulfonylurea and sitagliptin used in this study and these and other drugs, e.g. Glitazones, SGLT2 inhibitors etc documented in the literature.[29-51] The most cost effective combination of oral agents In USA is Metformin and Sulfonylurea Glimepiride because both these drugs are available in generic formulation. Moreover, these drugs ameliorate pathophysiologic mechanisms responsible for induction of hyperglycemia, e.g. insulin resistance and decline in insulin secretion. Metformin improves the sensitivity of both endogenous and exogenous insulin while Glimepiride enhances meal stimulated insulin secretion and may also blunt insulin resistance.[52-58] Alternatively, these drugs are more effective even when used as monotherapy in improving glycemic control in comparison to other approved oral agents.[59,60] Finally, these drugs complement the effects of each other and are more effective in achieving desirable glycemic control with lesser daily dose of insulin when compared with monotherapy as well as with combination of any other 2 oral drugs.[29-51] It is also apparent that the daily dose of basal insulin either Toujeo or Lantus may not be limited to 0.5 Units/ kg BW as previously well documented and in contrast to recent suggestions.[29-51,61,62]

The documentation of fewer hypoglycemic events and less or no weight gain using insulin Toujeo in comparison to insulin Lantus in this study confirms similar data in Edition' trials.[1-10] Moreover, it is apparent that both the prevalence of overall hypoglycemia and the degree of change in body weight were of lesser magnitude in this study following administration of insulin Toujeo in AM as compared to ' Edition' trials using insulin Toujeo in PM[1-10], a finding similar to the observation noted on administration of Insulin Lantus in AM as compared to bedtime.[13-17] Moreover, the absence of nocturnal hypoglycemia with administration of insulin in AM is distinctly safer in both groups. Thus, these benefits regarding incidence of hypoglycemia and body weight with treatment with insulin Toujeo over insulin Lantus may be attributed to a significantly lower (8.2 ± 0.5%) daily dose of insulin Toujeo in comparison to Insulin Lantus. The reasons for the discrepant finding regarding daily insulin dose in this study in contrast to the 'Edition' trials in which Insulin Toujeo dose was about 10- 15% higher may be the use of the combination of the same oral drugs in the same daily doses in both groups. Alternatively, the timing of administration of insulin may have contributed to this discrepant finding. In this study, both insulins were administered in AM whereas a 'Edition' trials in subjects with type 2 diabetes, they were injected exclusively in PM. We believe that a more consistent and uniform basal pattern of Insulin Toujeo as compared to insulin Lantus may account for the benefits of lower hypoglycemic events and the body weight on administration in AM compared to PM. AM administration of insulin Toujeo is likely to be more effective in controlling ' Dawn phenomenon' induced morning hyperglycemia in response to rises in counter regulatory hormones, e.g. cortisol, growth hormone, glucagon and catcholamines on awakening because of the continuing basal pattern during 20-24 hours after administration.[63] Moreover, the basal pattern lasting 24 hours is more akin to normal basal pattern and the longer duration of action of up to 30 hours. may be responsible for the lower daily dose of insulin Toujeo administered in AM in comparison to insulin Lantus as well as its administration in PM. Finally, basal pattern continuing during 20-24 hours and the duration of action lasting up to 30 hours after PM administration of insulin Toujeo and the declining levels of circulating counter regulatory hormones to their nadir during the late evening hours may contribute to the greater prevalence of nocturnal hypoglycemia noted in Edition trials as compared this study with AM administration. Continuous Glucose Monitoring study (CGMS) may be more appropriate to examine this hypothesis.

Therefore, in final analysis, this study shows that Insulin Toujeo may be as or more effective and safer than its administration in PM as well as insulin Lantus administered either in AM or PM. A clinical trial in a large population of subjects using a crossover design in a randomized sequence regarding the time of administration, AM vs PM while using the same oral drugs in the same daily dose is likely to eliminate impact of several factors including variability of individual insulin sensitivity and is therefore in order to examine the findings in this study.

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