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Soliqua (Lixi Lan): Sustained Long Term Cost Efficacy and Safety When Used in Combination with Metformin and Glimepiride

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Previous studies using basal insulin documented the lowest daily dose and least hypoglycemic events when combined with Glimepiride and Metformin while attaining desirable glycemic control. However, Pivotal trials with Soliqua excluded Glimepiride as a part of therapy as well as subjects with moderate obesity (BMI > 35kg/m2). Moreover, these trials were relatively short term.
Objective: Assess long term efficacy and safety of Soliqua in combination with Glimepiride and Metformin in subjects with type 2 diabetes irrespective of BMI in 'real world' experience.
Subjects: 30 adults with type 2 diabetes, age range 32-72 years with HbA1C >7.5% while receiving therapy with 1) Glimepiride, Metformin and Basal insulin and 2) Metformin and/or DPP 4 inhibitors and/or other SUs and /or GLP1 RA and/or Basal insulin and/or prandial insulin. Type 2 diabetes was confirmed by presence of C-peptide. Subjects with history of gastroparesis, Triglycerides over 300 mg/dl and pancreatitis were excluded. Subjects with elevated liver enzymes, over 2.5 times normal and EGFR < 30 ml/min were excluded as well.
Methods: All prior therapies were discontinued. All subjects were started on Glimepiride 8 mg, Metformin 1000-2000 mg and SC Soliqua was initiated prior to breakfast with daily dose 15 or 30 units as recommended. Daily dose was increased by 2 units every 3 days until AM fasting plasma

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glucose of 80-130 mg/dl was attained or the dose of 60 units was reached. The stable daily dose of Soliqua was continued until the time of analysis. Comparisons were conducted between body weights (kg), fasting plasma glucose (FPG) and HbA1C prior to initiation of combination therapy (pre Rx) and every 3-6 months until the time of analysis (post Rx).

Results: BMI ranged between 22-67 kg/m2. Duration of diabetes was 5-25 years. Duration of therapy with the combination therapy range, 7-56 months. Subjects were divided into 2 groups according to desirable HbA1C levels as per recommendations by ADA: 1) desirable HbA1C is < 7.0%, 2) desirable HbA1C 7-8 %. Both Fasting plasma glucose (mg/dl) and HbA1C (%) declined from 167 ± 10 and 9.7 ± 0.8 to 114 ± 4 and 7.6± 0.3 at the time of analyses (post Rx) respectively in the whole cohort. In 4 (0.13 %) morbidly obese subjects, FPG and HbA1C levels declined though not achieving desirable glycemic goals despite receiving maximal daily dose, 60 units of Soliqua. All four belonged to group 1. In the remaining 17 subjects desirable glycemic levels were attained and maintained. In group 2, desirable glycemia was reached in all 9 subjects. Symptomatic hypoglycemic events confirmed by blood sugar <70 mg/dl were reported by 4 subjects, none requiring secondary assistance. No severe hypoglycemia was reported. Mean daily dose of Soliqua was lower when compared to the pivotal trials.

Conclusion: Soliqua is effective and safe in the long term in all subjects irrespective of BMI when administered in combination with Glimepiride and Metformin. Moreover, lesser daily dose required to attain desirable glycemia with this oral combination may render it to be effective without attaining maximum daily dose in subjects with higher BMIs documented in pivotal trials using Metformin alone.

Keywords: Metformin; glimepiride; hypoglycemia; insulin monotherapy.

1. INTRODUCTION

We have previously documented attainment of desirable glycemic control with administration of premixed 70/30 insulin(Novomix, Novo Nordisk Pharmaceuticals Inc, Bagsværd, Denmark) as well as basal insulin glargine e.g. Lantus or Toujeo (Sanofi Pharmaceuticals Inc, Bridgewater, New Jersey) in conjunction with sulfonylurea Glimepiride and Metformin in subjects with type 2 diabetes [1-3]. This finding is confirmed by several other studies as well [4-11]. Moreover, daily dose of basal insulin was lower when used with this combination as compared to the daily dose when injected with oral monotherapy or with combination of agents without inclusion of SU Glimepiride [1,8-11]. It is apparent that the lower daily dose of insulin with combination of Glimepiride and Metformin was also probably responsible for lesser hypoglycemic events and weight neutrality or minimal weight gain in comparison to combinations of oral agents not including Glimepiride [1-11]. However, pivotal clinical trials using combination of basal insulin glargine and GLP 1 RA Lixesanatide in a fixed proportion 100 units/33 mcg (Soliqua, Sanofi Pharmaceuticals Inc.) excluded Glimepiride as one of the oral agents as a part of adjunctive therapy [12-18]. Moreover, these trials excluded subjects with moderate to morbid obesity (BMI > 35kg/m2) as well. Finally, these pivotal clinical trials were conducted over relatively short term period of 24-52 weeks [12-18]. Therefore, we examined long term efficacy and safety of Soilqua in combination with Glimepiride and Metformin in subjects with type 2 diabetes irrespective of degree of obesity (BMI 28-45 kg/m2) in 'real world' experience.

2. SUBJECTS AND METHODS

Electronic medical records of 30 adults, 14 men and 16 women with type 2 diabetes, age range 32-72 years receiving Soliqua were reviewed in June 2021. Subjects were referred to endocrinology clinic at an academic center because of lapse of glycemic control (HbA1C >7.5%). At the time of initial consultation visit, therapy for diabetes included 1) Glimepiride, or Glipizide and/or Metformin and Basal insulin, 2) DPP 4 inhibitors in maximum approved daily dose and/or Metformin and/or SU, 3) SU and /or Metformin and daily or weekly GLP1 RA and 4) Basal and prandial insulins with no oral agents. Daily doses of Glimepiride, Glipizide and Metformin were 4-8 mg, 20-40mg and 1000-2000 mg respectively. Type 2 diabetes was confirmed by presence of C-peptide. Subjects with history of gastroparesis and pancreatitis were excluded. Exclusion criteria also included EGFR < 30 ml/min, elevated liver enzymes > 2.5 times highest normal level and Triglycerides over 300 mg/dl. Basal insulin, oral agents other than

Glimepiride and Metformin, prandial insulin and GLP1 RA were discontinued. All subjects were administered Glimepiride 8 mg and Metformin 1000-2000 mg and Soliqua was initiated with daily dose, 15 or 30 units in AM prior to breakfast depending on the previous basal insulin dose as recommended in the label and used in the previous studies [12-18]. Initial Daily dose in subjects who had never received insulin was 15 units. All subjects were instructed to administer Soliqua in AM around the same time daily. The dose was increased by 2 units every 3 days until AM fasting plasma glucose >80<130 mg/dl was attained or the dose of 60 units was reached. In subjects not achieving desirable glycemic goals despite receiving maximal approved daily dose (60 units), Soliqua was discontinued and alternative approved therapy was initiated. In the remaining subjects, the daily dose of Soliqua was continued until the time of analysis. Hypoglycemic events were reported only if the blood sugars were < 70 mg/dl in presence of symptoms including a change in mental status or blood sugar <54mg/dl with or without symptoms. Comparisons were conducted between body weights (kg), fasting plasma glucose (FPG) and HbA1C prior to initiation of combination therapy (pre Rx) and every 3-6 months until the time of analysis (post Rx). Desirable glycemic control was expressed by HbA1C levels according to guidelines recommended by American Diabetes Association for individual subject. Thus, subjects were divided into 2 groups according to desirable HbA1C levels: as per recommendations by ADA: 1) desirable HbA1C is < 7.0%, 2) desirable HbA1C 7-8 %. All laboratory tests were conducted by the local laboratory at the medical center with established commercial kits. Statistical analyses for comparisons were conducted by Student's 't' test, analyses of variance. Correlations were examined by linear regression analysis between declines in HbA1C levels on one aspect and age, duration of diabetes and baseline C-peptide concentrations on the other. All data are presented as Mean ± SEM.

3. RESULTS

BMI, duration of diabetes and duration of the combination therapy in 30 subjects who continued to receive Soliqua ranged between 22-67 kg/m2 (mean 38± 8), 4-24 years (mean 12± 5) and 9-60 months (mean 21± 8) respectively. Mean fasting plasma glucose concentrations prior to initiation of therapy declined significantly following treatment with the combination therapy from 167±15 to 118± 4 mg/dl whereas HbA1C dropped from 9.7±0.8 to 7.6±0.3 % within 3-6 months in the whole cohort of 30 subjects (Table 1). In 4 (0.13 %) morbidly obese subjects, fasting plasma glucose and HbA1C levels declined though not achieving desirable glycemic goals despite receiving the maximal daily dose, 60 units of Soliqua. All four belonged to group 1. In these subjects, mean HbA1C prior to initiation of triple therapy was 10.2 ± 0.6% and declined to 8.5 ±0.3% within 6 months. Desirable HbA1C (7.0 %) levels were attained and maintained till the time of analysis in the remaining 17 subjects in group 1 (Table 2). In group 2, desirable HbA1C (7- 8 %) were attained and maintained in all 9 subjects (Table 3). Symptomatic hypoglycemic events confirmed by blood sugar <70 mg/dl were reported by 4 subjects in group 1, none requiring secondary assistance and none in group 2. No severe hypoglycemia as defined by requiring secondary assistance for resuscitation or blood sugar < 54 mg/dl was reported. Mean daily dose of Soliqua in subjects was lower; 0.38±0.08 units/kg BW compared to the previous trials; 0.46units to 0.54 units /kg BW (12-20). Finally, correlations between declines in HbA1C on one hand and age, duration of diabetes, BMI and C-peptide levels prior to initiation of triple therapy on the other aspect were not statistically significant.

4. DISCUSSION

This study demonstrates that desirable glycemic control was attained within 3-6 months following administration of Soliqua when used in combination with Metformin and Glimepiride. This finding is consistent with the data in several previous clinical trials using Metformin alone as an oral agent over a short term period of 24-30 weeks [12-19]. This study also documented efficacy of Soliqua irrespective of the age, duration of diabetes and antecedent beta cell function as evident in previous studies [15,18]. Finally, the findings of lack of significant weight gain (weight neutrality) as well as hypoglycemic events noted in this study are also consistent with the previous reports [12-19].

However, several differences are evident between this study and previous trials. This study used Glimepiride in addition to Metformin whereas previous trials used Metformin alone. This study included morbidly obese subjects in contrast to previous trials in which subjects with BMI >35 kg/m2 were excluded. Moreover, the duration of sustained glycemic control is

Table 1. Daily dose of Soliqua, body weight, fasting plasma glucose [FPG] and HbA1C prior to (Pre Rx) and following combination therapy in 30 subjects at 3-6 months (Post Rx)

	Daily dose u/kg	Body weight kg	FPG mg/dl	HbA1C %
Pre Rx	0	96 ± 3	167 ± 10	9.7 ± 0.8
Post Rx 1 ǂ	0.40 ± 0.03	94 ± 3	114 ± 4*	7.6 ± 0.3

**p< 0.01 vs Pre Rx*
ǂ 3-6 months Post Rx

Table 2. Daily dose of Soliqua, body weight, fasting plasma glucose [FPG] and HbA1C prior to [Pre Rx] and following [Post Rx] combination therapy in 17 subjects in Group 1

	Daily dose u/kg	Body weight kg	FPG mg/dl	HbA1C %
Pre Rx	0	90 ± 6	170 ± 12	9.8 ± 0.4
Post Rx 1ǂ	0.38 ± 0.04	87 ± 6	113 ± 6*	6.9 ± 0.3* ǂ
Post Rx 2€	0.36 ± 0.04	87 ± 5	108 ± 6*	6.7 ± 0.2* ǂ

**p< 0.01 vs Pre Rx, ǂ Desirable HbA1C ≤ 7.0, ǂ 3-6 months Post Rx*
€ At time of analysis Post Rx

Table 3. Daily Soliqua dose, body weight, FPG and HbA1C in 9 subjects in group 2 prior to [Pre Rx] and after [Post Rx] therapy

	Daily dose u/kg	Body weight kg	FPG mg/dl	HbA1C %
Pre Rx	0	98 ± 7	173 ± 14	10.2 ± 0.4
Post Rx 1 ǂ	0.40 ± 0.05	94 ± 6	108 ± 7*	7.6 ± 0.3* ǂ
Post Rx 2€	0.41 ± 0.05	95 ± 6	116 ± 9*	7.5 ± 0.4* ǂ

**p< 0.01 vs Pre Rx, ǂ Desirable HbA1C 7-8, ǂ 3-6 months Post Rx, € At time of analysis Post Rx*

markedly longer in this study, up to 60 months in some subjects compared with 52 weeks in an isolated open label extension trial [19]. Finally and importantly, the daily dose of Soliqua in our study is markedly lower in comparison to previous trials [12-19].

Lower daily dose of Soliqua required to attain and maintain desirable glycemic control in this study is consistent with several other clinical trials using insulin with combination with Glimepiride and Metformin [1-11, 20-21]. Moreover, several studies have documented lower daily dose of insulin in combination with Glimepiride alone as compared to insulin monotherapy [22-27], and may be attributed to 1) enhanced endogenous insulin secretion and sensitivity induced by Glimepiride [20-21,28-31] and 2) improvement in sensitivity of both exogenous and endogenous insulins by Metformin [32,33]. Lesser daily dose of insulin also probably contributed to almost no hypoglycemia and no weight gain as documented in the literature [1-11,20-21,32-33]. Apparently, this study demonstrates that the lack of inclusion of SU, e.g. Glimepiride, in previous trials probably because of the fear of hypoglycemia may be overblown. Finally, we believe that the reduction in requirement of the daily dose achieved by inclusion of Glimepiride afforded its use in morbidly obese subjects without reaching the maximum approved daily dose and thus discontinuation.

5. CONCLUSION

Soliqua is cost effective and safe in the long term in all subjects irrespective of BMI, when administered in combination with Glimepiride and Metformin. Moreover, it may be useful when administered in this oral combination in more subjects with higher BMI without attaining maximum daily dose in comparison to Metformin alone documented in pivotal trials.

DISCLAIMER

The products used for this research are approved by regulatory agency for treatment of type 2 diabetes in our country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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