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Randomized Clinical Trial Assessing the Efficacy and Safety of Bromocriptine-QR when Added to Ongoing Thiazolidinedione Therapy in Patients with Type 2 Diabetes Mellitus

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Abstract

Aims: To evaluate the glycemic control efficacy and cardio-metabolic safety of bromocriptine- quick release (Bromocriptine-QR) among subjects with type 2 diabetes who were taking a thiazolidinedione (TZD) at baseline.

Methods: A subgroup from the Cycloset Safety trial who were taking a TZD at baseline with or without another oral anti-diabetes medication were randomized to receive additional once daily (morning) bromocriptine-QR (1.6 - 4.8 mg/day) or placebo for up to 52 weeks. Glycemic efficacy analyses were based on intent to treat modified (ITTm) and evaluable per protocol (EPP) population using general linear model after adjusting for baseline covariates and stratified by A1C level of <7.5 of ≥7.5. The odds ratio of participants achieving A1C ≤7% were calculated. Similar analyses for safety were performed on weight and hypoglycemia.

Results: In this trial 495 subjects were taking a TZD at baseline and 122 also had a baseline A1C of ≥7.5. For subjects with an A1C of ≥7.5, bromocriptine-QR treatment led to significant reduction in A1C (ITTm -0.81%, p=0.001and EPP -0.91%, p=0.002), fasting plasma glucose (ITTm -21.5 mg/dl, p=0.03 and EPP -20.5 mg/dl, p=0.05), and higher frequency achieving an A1C≤7% (32.1% vs. 15.9%, p=0.05) when compared with placebo. For subjects with a baseline A1C of <7.5, subjects randomized to bromocriptine-QR had a greater odds of having an A1C level of ≤7.0 (OR 2.74, 95% CI 1.45, 5.15; p =0.002). Treatment with bromocriptine-QR had no adverse impact on weight or risk of hypoglycemia.

Conclusion: Daily morning bromocriptine-QR added to ongoing TZD treatment for uncontrolled type 2 diabetes improved glycemic control and was well tolerated.

Keywords: Bromocriptine-QR; Thiazolidinedione; Type 2 diabetes; Hemoglobin A1c

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by defects in insulin sensitivity and insulin secretion [1]. Insulin resistance is manifested early in the natural history of the disease but glucose tolerance remains normal because of a compensatory increase in insulin secretion and hyperinsulinemia. With time, however, there is progressive beta cell failure leading to the development of impaired glucose tolerance and eventually overt T2DM [2,3]. Initial drug-induced improvement in glycemic control in patients with T2DM deteriorates over time requiring the use of additional antidiabetic medications with different modes of action [3]. There is now growing evidence that favors the use of interventions that improve insulin resistance and preserve beta cell function to treat T2DM [2-5]. Thiazolidinedione (TZD) therapy in patients with T2DM improves glycemic control both by augmenting beta cell function [6,7] and enhancing tissue sensitivity to insulin by acting as peroxisome proliferator-activated receptor (PPAR) gamma agonists in liver and muscle [8-10]. Nonetheless, the glycemic control often worsens over time if TZD therapy is initiated late in the course of the disease. The addition of agents that improve insulin sensitivity, via a different mechanism than the TZDs, may be beneficial in patients failing TZD therapy.

Animal studies indicate that reduced hypothalamic dopaminergic tone promotes insulin resistance and glucose intolerance [11-14]. Appropriately timed delivery of bromocriptine to the central nervous system has been shown to reduce insulin resistance and glucose intolerance [15]. A quick release formulation of bromocriptine (bromocriptine-QR), when given to T2DM subjects in the morning within 2 hours of waking, improves glycemic control primarily by reducing post-prandial glucose without raising post-prandial insulin levels suggesting enhanced postprandial responsiveness to insulin [16,17]. Bromocriptine-QR recently was approved by the US Food and Drug Administration (FDA) and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. As a centrally acting insulin sensitizer [11,15] bromocriptine-QR may have synergistic effects when added to beta cell preserving agents/peripherally acting insulin sensitizers such as TZDs. The overall safety, including cardiovascular outcomes, of bromocriptine-QR was assessed

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in a one year randomized clinical trial [18]. In addition to the overall safety and cardiovascular risk evaluation, additional analyses were pre-specified to assess the impact of bromocriptine-QR compared to placebo on glycemic measures among subgroups of the total subject population [19]. The purpose of this post-hoc analysis is to evaluate the effect of bromocriptine-QR on glycemic control after 52 weeks of treatment among participants who at baseline were treated with TZDs (with or without another OAA).

Participants and Methods

Study design-cycloset safety trial

The Cycloset Safety Trial was a 52-week, double blind, double dummy, multicenter trial. After a two-week lead-in period subjects were randomized 2:1 to usual diabetes treatment plus once daily (morning) bromocriptine-QR or placebo. The key elements and aspects of this study protocol were published previously [20]. The Cycloset Safety Trial was designed to enroll a broad population of participants with T2DM. Eligible participants had T2DM for at least 6 months, were on a stable T2DM regimen for at least 30 days prior to randomization consisting of either diet only or up to 2 anti-diabetes agents (one or two oral T2DM agents; insulin alone; or insulin in combination with an oral diabetes agent), had an A1C level ≤ 10.0% and were between 30 and 80 years of age. Exclusion criteria included current chronic use of prescription sympathomimetic drugs, ergot alkaloid derivatives or abortive migraine medications; or clinically significant co-morbid conditions such as uncontrolled hypertension, New York Heart Classification III-IV congestive heart failure (class I-II were allowed in the study), advanced renal failure or cancer within the past five years (other than non-melanoma skin or non-metastatic prostate cancer).

The study was conducted at 74 sites across the U.S., including 19 Veterans Affairs (VA) hospitals and 55 non-VA centers. An independent data safety and monitoring board met quarterly and reviewed unblinded data. Overall study oversight was by a steering committee consisting of two academic principal study investigators, scientific members of the study sponsor, members responsible for site management coordination (Clinical Research Management Inc., Agawam, MA and Veterans Affairs Cooperative Studies Program Center, Boston, MA), and members of the data and statistical coordinating center (EVEREST Inc., Toronto, CA) and independent data safety and monitoring board.

After randomization, drug therapy was initiated with one 0.8 mg bromocriptine-QR or placebo tablet and titrated at a rate of 1 tablet (active or matching placebo) per week until a maximal tolerated dose of at least 2 tablets (1.6 mg/day) or a maximum of 6 tablets (4.8 mg bromocriptine-QR) per day was achieved. After titration, subjects remained on their maximal daily dose for a total of 52 weeks from randomization. Subjects continued on their baseline T2DM agents during the first 3 months of the study but study investigators were allowed to alter the subjects' dosages to optimize T2DM control as deemed appropriate in accordance with the 2004 American Diabetes Association treatment recommendations [21]. After 3 months, dosage adjustments and alterations in the T2DM drug regimen (elimination or addition of another OAA) were allowed if deemed necessary but could not include additions that resulted in a final concomitant anti-diabetes regimen that exceed two OAA or insulin plus one oral agent. Two physicians blinded to treatment assignment determined whether or not study subjects changed accordingly their concomitant anti-diabetes medications. The study protocol was approved by the appropriate review boards for each site and all participants provided a written informed consent to participate. The study was performed in accordance with the Declaration of Helsinki.

Participant selection criteria

For this post-hoc analysis of bromocriptine-QR efficacy and safety, a subset of subjects of the total study population from the Cycloset Safety Trial was selected among those who at baseline were taking a TZD (alone or in combination with another OAA).

Study Evaluations

Efficacy and safety assessments

A1C and fasting plasma glucose were measured at weeks 0, 12, 24, 36 and 52. Data on adverse experiences, physical examinations, vital signs and body weight were collected at each study visit. All adverse experiences were rated by investigators for intensity and relationship to study drug. All serious adverse events were independently adjudicated. Laboratory evaluations included blood chemistries, hematology and urinalysis which all were performed by a central laboratory using their standard operating procedures (ACM Laboratories, Rochester, NY).

Statistical analyses

The aim of this analysis was to evaluate the between group change from baseline to week 52 in A1C for those not adequately controlled on TZD therapy defined as a baseline A1C of ≥7.5 and the odds of having an A1C of ≤ 7.0 after 52 weeks for those subjects with a baseline A1C of < 7.5. Efficacy analyses were performed on the intent to treat population consisting of all randomized participants who received at least one dose of study drug and who had both a baseline and at least one post-baseline measurement (Intent to Treat Modified [ITTm] population). Rosiglitazone equivalent dosages were assigned for subjects treated with pioglitazone such that 2, 4, and 8 mg of rosiglitazone equaled 15, 30, and 45 mg of pioglitazone, respectively. The Chi Square test was used to test differences between categorical variables and general linear models were used to calculate the between group difference (95% confidence interval (CI)) in A1C and fasting glucose from baseline to week 52 for bromocriptine-QR. Analysis of changes in A1C was stratified by baseline A1C of <7.5 and ≥7.5 and were adjusted for baseline A1C as well as for age, race/ethnicity, presence of concurrent OAA, medication intensification (defined as an increase in the dose of OAA medication or the addition of another OAA; or addition of insulin during follow-up), baseline rosiglitazone equivalent dose and duration of T2DM. For subjects with A1C of ≥7.5, changes in A1C were also stratified by the presence and absence of OAA intensification. The frequency of participants who achieved an A1C of ≤ 7% was assessed using Chi Square test. Logistic regression was used to calculate the odds ratio (95% CI) of achieving an A1C of ≤ 7% among participants taking bromocriptine-QR compared to placebo while adjusting for the covariates described above. Missing values of A1C were handled using the last observation carried forward (LOCF) method.

Changes in body weight was assessed for the entire group and stratified by baseline A1C of <7.5 and ≥7.5.

For subjects with a baseline A1C of ≥ 7.5 the impact of therapy on glycemic control (A1C and fasting glucose) based on the above described methods was assessed on the pre-specified evaluable per protocol (EPP) population defined as those subjects who were at least 80% compliant with prescribed dosing of study drug and completed 52 weeks of the study without any major protocol violations during the trial.

All statistical analyses were conducted using SAS software version 8.2 (Cary, NC).

Results

Of the 3070 subjects randomized 2:1 to bromocriptine QR or placebo in the Cycloset Safety Trial, 495 were taking a TZD at baseline. Of these 495, 373 subjects had a baseline A1C <7.5 % (254 on bromocriptine-QR and 119 on placebo) and 122 subjects had a baseline A1C ≥7.5 % (78 on bromocriptine-QR and 44 on placebo). Of the 495 participants, 190 (57%) bromocriptine-QR and 117 (72%) placebo subjects completed 52 weeks of treatment. Reasons for discontinuation of therapy included adverse events: 21% bromocriptine-QR, 13% placebo; withdrawal of consent: 11% bromocriptine-QR, 6% placebo; lost to follow up: 4% bromocriptine-QR, 3% placebo; other: 2% bromocriptine-QR, 4% placebo; protocol deviation: 2% bromocriptine-QR, 1% placebo: and sponsor or PI decision: 2% bromocriptine-QR, 2% placebo.

Baseline demographic and clinical characteristics (Table 1) for 495 subjects stratified by baseline A1C (≥7.5 and <7.5). Similar baseline A1C were observed in study participants taking bromocriptine-QR and placebo in both the ≥7.5 baseline group (8.2 ± 0.6% vs. 8.4 ± 0.7%, respectively) and the <7.5 baseline group (6.5 ± 0.6% vs. 6.4± 0.6% respectively). Among subjects with baseline A1C ≥ 7.5, the majority of bromocriptine-QR treated participants (83%) and placebo treated participants (82%) were taking another OAA in addition to a TZD. More participants were taking rosiglitazone at baseline compared to pioglitazone in both treatment arms (71% for bromocriptine-QR and 59% for placebo). The baseline rosiglitazone equivalent dose of TZD was similar in both groups (5.3 ± 2.3 mg in the bromocriptine-QR arm vs. 5.9 ± 2.2 mg in the placebo arm).

Glycemic control

Overall when added to a TZD, bromocriptine-QR produced significant improvements in glycemic control. For subjects with a baseline A1C level of ≥7.5 the between group difference in change from baseline in A1C was significant. (Figure 1, Table 2). Using ITTm analysis, after controlling for baseline demographic and clinical characteristics, including baseline glycemic control and changes in concomitant OAA, the between group reduction (95% CI) from baseline in A1C was -0.81% (-1.30%, -0.33%; p=0.001) for participants randomized to bromocriptine-QR compared to placebo (Table 2) while for fasting plasma glucose was -21.5 mg/dl (-41.0 mg/dl, -1.9 mg/dl; p=0.03). Relative to participants randomized to bromocriptine-QR, more participants randomized to placebo increased the dose of a concomitant OAA (41% versus 27%, P = 0.04) or added a new OAA or insulin (18% versus 8%, p = 0.03) (Figure 2). Even though placebo-treated participants intensified their antihyperglycemic regimen more frequently, participants on bromocriptine-QR achieved better glycemic control over the 52 week treatment period. Stratified by intensification of therapy, the between group difference in A1C change was -0.82% (-1.47%, -0.18%) among participants who did not intensify therapy and -0.96% (-1.76%, -0.16%) among participants who did intensify therapy. For fasting plasma glucose and stratified by intensification therapy, the reduction was -23.5 mg/dl (-49.2 mg/dl, 2.1 mg/dl) among participants who did not intensify therapy and -28.6 mg/dl (-62.1 mg/dl, 5.0 mg/dl) among participants who did intensify therapy. A greater percentage of participants achieved an A1C ≤ 7% with bromocriptine-QR (32.1%) than with placebo (15.9%) (P = 0.05). After controlling for the multiple covariates described herein, the odds ratio (95% CI) of achieving a A1C ≤ 7% among participants taking bromocriptine-QR compared to placebo was 3.33 (1.12, 9.99) (p = 0.03).

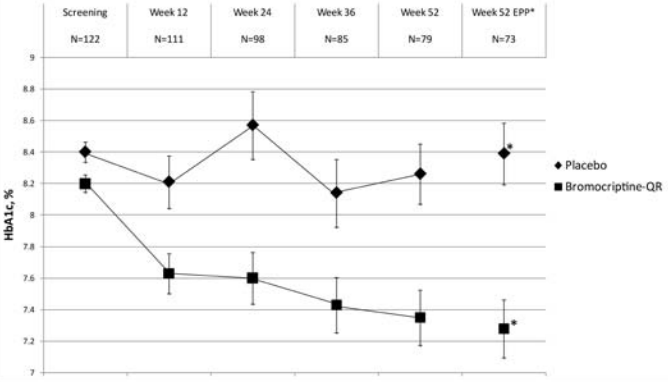

Figure 1: Change over time in percent A1C by treatment group Among Subjects with a Baseline A1C of ≥ 7.5. The average A1C for subjects receiving bromocriptine-QR (squares) and placebo (diamonds) are depicted at each study visit for subjects that had an HbA1c measured. Overall there is a significant decline in A1C for those subjects randomized to bromocriptine-QR compared to no change after 52 weeks for those subjects randomized to placebo. EPP Analysis: Data represent those subjects completing 52 weeks of the study and being at least 80% compliant with prescribed dosing of study drug over the course of the trial. *The Week 52 EPP data point depicts the average A1C after adjusting for baseline hemoglobin a1c, age, race/ethnicity, presence of concurrent oral antihyperglycemic medication, change of antihyperglycemic medication during follow-up, baseline rosiglitazone equivalent dose, and duration of diabetes mellitus. The between group difference for change from baseline in A1C for bromocriptine-QR versus placebo subjects was -0.91% (-1.47%, -0.35%; p = 0.002).

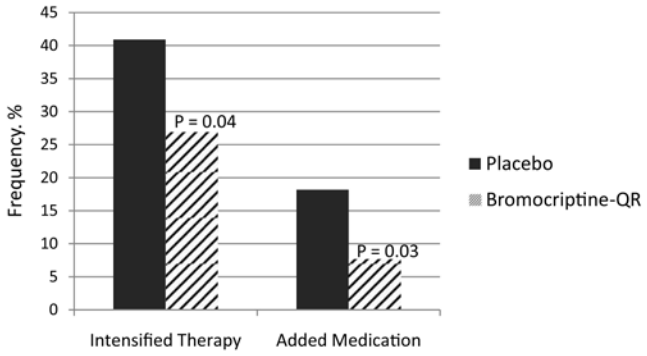

Figure 2: Antihyperglycemic medication changes during the course of the study by treatment group Among Subjects with a Baseline A1C of ≥ 7.5. Relative to participants randomized to bromocriptine-QR (solid bar), more participants randomized to placebo (striped bar) increased the dose of a concomitant oral antihyperglycemic agent (OAA); 41% versus 27%, P = 0.04 or added a new OAA or insulin; 18% versus 8%, p = 0.03. Even though placebo-treated participants intensified their antihyperglycemic regimen more frequently, participants on bromocriptine-QR achieved better glycemic control over the 52 week treatment period.

The results of the intervention on A1C and fasting glucose for the EPP analysis were similar to the ITTm analysis. In the fully adjusted model the between group difference for change from baseline in A1C and fasting glucose levels for bromocriptine-QR versus placebo subjects were -0.91% (-1.47%, -0.35%; p = 0.002) and -20.5 mg/dl (-41.1 mg/dl, 0.0 mg/dl; p = 0.05), respectively.

Among subjects with an A1C of <7.5, the change from baseline in A1C in the ITTm analysis for both groups was small (bromocriptine-QR 0.14 (0.04, 0.24) vs. placebo 0.29 (0.14, 0.44) likely due to the low

	Baseline A1C ≥ 7.5		Baseline A1C <7.5	
Characteristics	Bromocriptine-QR (N = 78)	Placebo (N = 44)	Bromocriptine-QR N = 254	Placebo N = 119
Age	56.4 ± 11.0	59.6 ± 10.9	59.9 ± 9.8	58.7 ± 10.3
% Female	52.6	43.2	57.5	24.0
Race/Ethnicity % White % Black % Hispanic % Other	 62.8 16.9 15.4 3.8	 70.5 9.1 15.9 4.5	 66.9 16.9 13.4 2.8	 76.5 14.3 8.4 0.8
Weight, kg	94.4 ± 19.4	95.5 ± 20.5	94.3 ± 17.3	97.4 ± 19.2
Body Mass Index, kg/m^2	32.9 ± 5.1	32.7 ± 5.2	33.1 ± 5.1	33.6 ± 4.8
Duration of diabetes mellitus, years	7.8 ± 7.5	9.3 ± 7.6	6.9 ± 6.0	6.2 ±4.2
Screening thiazolidinedione % Rosiglitazone % Pioglitazone	 71.0 29.0	 59.0 41.0	 45.3 54.7	 42.9 57.1
Baseline Rosiglitazone Equivalent Dose, mg	5.3 ± 2.3	5.9 ± 2.2	5.1 ± 2.3	5.4 ± 2.4
Hemoglobin A_{1c},%	8.2 ± 0.6	8.4 ± 0.7	6.5 ± 0.6	6.4 ± 0.6
Fasting plasma glucose, mg/dl	172 ± 39.7	175 ± 44.1	125 ± 25	126 ± 26
Systolic Blood Pressure, mmHg	129 ± 13.4	131 ± 14.3	129 ± 14	128 ± 13
Diastolic Blood Pressure, mmHg Baseline Diabetic Therapy at Baseline	76.9 ± 7.9	76.9 ± 9.6	77 ± 8	77 ± 9
% Taking thiazolidinedione only % Taking TZD with Metformin % Taking TZD with Sulfonylurea % Taking TZD with Other Oral Diabetes Med	17 60 22 3	18 43 39 2.3	37 50 14 0.4	40 30 4 0.8

Data presented as mean ± standard deviation (unless otherwise specified)

Table 1: Baseline demographic and clinical characteristics of the study population.

	Glycemic Control Parameter	
	HbA1c, % (95% CI)	**Fasting Plasma Glucose, mg/dl (95% CI)**
Adjusted for baseline glycemic measure†		
Bromocriptine-QR	-0.62 (-0.90, -0.34)	-10.4 (-21.9, 1.1)
Placebo	0.04 (-0.33, 0.42)	4.6 (-10.7, 19.9)
Between group difference	-0.66 (-1.13, -0.19); p < 0.01	-15.0 (-34.1, 4.1); p = 0.12
Fully adjusted model‡		
Bromocriptine-QR	-0.67 (-0.96, -0.39)	-12.7 (-24.1, -1.3)
Placebo	0.14 (-0.24, 0.52)	8.7 (-6.6, 24.1)
Between group difference	-0.81 (-1.30, -0.33); p =0.001	-21.5 (-41.0, -1.9); p = 0.04

*ITTm analysis: modified intent to treat – all subjects treated that had one post randomization laboratory measure, missing week values of HbA1c and fasting plasma glucose were handled using the last observation carried forward method

†Adjusted for baseline glycemic measure: Model controlled for baseline HbA1c for the HbA1c outcome and for baseline Fasting Plasma Glucose for the Fasting Plasma Glucose outcome

‡Fully adjusted model: Model controlled for baseline glycemic measures (% for HbA1c and mg/dL for fasting glucose), age (years), race/ethnicity (white, black, Hispanic, other), presence of concurrent oral antihyperglycemic medication (yes/no), whether the dose of antihyperglycemic medication was adjusted during follow-up (increase, decrease, same), whether additional antihyperglycemic medication was added during follow-up (yes/no), baseline rosiglitazone equivalent dose (mg), and the duration of diabetes mellitus (years)

Table 2: Effect of Bromocriptine-QR on Change from baseline to week 52 for HbA1c and Fasting Plasma Glucose (ITTm) among Subjects with Baseline A1c of ≥ 7.5*.

average starting A1C of 6.4 (Table 3). However a greater proportion of subjects on bromocriptine-QR (83%) vs. placebo (72%) met the A1C goal of ≤7.0 at week 52. The odds of meeting the ADA A1C goal of ≤7.0 after 52 weeks adjusted for baseline A1C level and the fully adjusted model was greater for subjects that added bromocriptine-QR (OR 2.67; 95% CI 1.46, 4.88; p =0.002 and 2.74; 95% CI 1.45, 5.15; p =0.002; respectively) as compared to placebo. Similar results were obtained for the EPP treatment population.

Changes in weight

At baseline there was no difference between the treatment groups in BMI in those with either A1C ≥7.5 or <7.5 at baseline. Among all participants in the study, over the 52 week trial, there was no statistically significant difference in the between group change from baseline in weight for the EPP population that stayed on treatment after adjustment for baseline weight (bromocriptine-QR vs. placebo: -0.26 kg (-1.47 to 0.95); p= 0.68). In a subgroup analysis, among subjects with an A1C of ≥7.5 at baseline, the placebo arm experienced an increase in weight by 2.26 kg (95% CI: 0.19 to 4.35 p=0.03) whereas weight in the bromocriptine-QR participants did not change (-0.22 kg, 95% CI: -2.06 to 1.61; p =0.81). However the between group difference of -2.47 kg (95% CI: -5.23 to 0.29) was not statistically significant (p = 0.08). Similarly in an EPP population among subjects with an A1C of <7.5 at baseline between group difference of 0.25 kg (95% CI: -1.08 to 1.58) was not statistically significant (p = 0.7).

Tolerability

Among all study participants, common adverse events among

Population	Adjusted Baseline A1C	Fully adjusted model‡
Intent to Treat*	*Change in A1C (95% confidence interval)*	
Bromocriptine-QR, N = 254	0.13 (0.03, 0.23)	0.14 (0.04, 0.24)
Placebo, N = 119	0.30 (0.15, 0.45)	0.29 (0.14, 0.44)
Between group difference change from baseline in A1C	-0.17 (-0.35, 0.001); p =0.06	-0.15 (-0.33, 0.002); p =0.09
	Odds Ratio (95% confidence interval)	
A1C Goal of ≤ 7.0at week 52	2.67 (1.46, 4.88); p =0.002	2.74 (1.45, 5.15); p =0.002
Evaluable Per Protocol	*Change in A1C (95% confidence interval)*	
Bromocriptine-QR, N = 147	0.16 (0.05, 0.27)	0.15 (0.04, 0.27)
Placebo, N = 85	0.33 (0.18, 0.48)	0.34 (0.19, 0.48)
Between group difference change from baseline in A1C	-0.17 (-0.35, 0.002); p =0.08	-0.18 (-0.37, 0.001); p =0.06
	Odds Ratio (95% confidence interval)	
A1C Goal of ≤ 7.0 at week 52	2.40 (1.17, 4.90); p =0.02	2.60 (1.25, 5.42); p =0.01

*ITTm analysis: modified intent to treat – all subjects treated that had one post randomization laboratory measure, missing week values of A1C and fasting plasma glucose were handled using the last observation carried forward method

‡Fully adjusted model: Model controlled for baseline glycemic measures (% for A1C and mg/dL for fasting glucose), age (years), race/ethnicity (white, black, Hispanic, other), presence of concurrent oral antihyperglycemic medication (yes/no), whether the dose of antihyperglycemic medication was adjusted during follow-up (increase, decrease, same), whether additional antihyperglycemic medication was added during follow-up (yes/no), baseline rosiglitazone equivalent dose (mg), and the duration of diabetes mellitus (years)

Table 3: Effect of Bromocriptine-QR on Change from baseline to week 52 for HbA1c ands Odds of Meeting Goal A1C of ≤ 7.0 Among Subjects with Baseline A1C of < 7.5.

those randomized to bromocriptine-QR that occurred at a rate of ≥ a 2 percentage point difference from placebo included nausea (44% vs. 7%), vomiting (9% vs. 1%), fatigue (14% vs. 10%) and headache (12% vs. 6%). In contrast, events occurring less often with bromocriptine-QR compared to placebo included weight gain (3% vs. 5%). Edema was similarly reported in both groups at 9%. The discontinuation rate due to adverse events for bromocriptine-QR and placebo-treated subjects was 21% and 13%, respectively. Fractures were reported equally in both groups at 3%. There were seven events of hypoglycemia reported in the bromocriptine-QR arm, six among those with A1C <7.5, and one reported in the placebo arm with A1C ≥7.5. None of the hypoglycemic events in the bromocriptine-QR-treated group were described as severe or serious. One event of hypoglycemia was reported in the placebo-treated group and was described as severe and serious. Implicating factors other than bromocriptine-QR were present among 5 of the subjects reporting hypoglycemia (1 subject had stopped bromocriptine-QR prior to the event, two subjects increased their sulfonylurea dose just prior to the event, another subject's event occurred upon increasing the bromocriptine-QR dose to 4 tablets per day so it was decreased to three without further hypoglycemic events and one subject had not eaten all morning).

Safety

Among all participants in the study, 26 subjects in the bromocriptine-QR treated group (7.8%) reported 33 serious adverse events while the placebo-treated group had 13 subjects (7.9%) reporting 14 serious adverse events. In the cardiac disorders body system class there were nine events (3%) in the bromocriptine-QR group and seven (4.3%) in the placebo group. No other body system classes had events occurring in greater than 2% of either group.

Discussion

Among participants with suboptimal glycemic control who were taking a TZD with or without another oral anti-diabetes medication, the addition of bromocriptine-QR resulted in a sustained improvement in A1C over 52 weeks of treatment. For subjects with a baseline A1C of ≥ 7.5, the between group difference in change from baseline on A1C was significantly reduced for those subjects receiving bromocriptine-QR (ITTm -0.81% and EPP -0.91%) and three times as many subjects reached a goal A1C of ≤ 7.0, after accounting for various baseline covariates and adjusting for the greater tendency of the placebo arm to intensify their diabetes regimen. Similarly, for subjects with a baseline A1C of <7.5, subjects were more likely to the meet the A1C goal of ≤7.0 after 52 weeks when treated with bromocriptine-QR. Regardless of incoming A1C level, the addition of bromocriptine-QR safely improved overall glycemic control when compared to standard of care. Inasmuch as the majority of subjects (90%) in this analysis were taking TZDs and another OAA medication at baseline, the findings described herein suggest that bromocriptine-QR elicits such effects in subjects on a TZD plus another OAA medication. There was no statistically significant increase in weight among participants who took a TZD and bromocriptine-QR and this combination was well tolerated.

Insulin resistance and beta cell dysfunction are the key contributors to the pathogenesis of T2DM [2,22,23]. Therapies that improve insulin resistance have been demonstrated to delay the progression of impaired glucose tolerance to overt T2DM [24,25] and delay the time to initiation of insulin therapy among participants with T2DM [3,6,26]. Current guidelines for T2DM treatment advocate a stepwise approach that relies mainly on the initial therapy with metformin and/or sulfonylurea [27]. However, these therapies do not preserve beta cell function long term and glycemic control in T2DM patients treated with these therapies deteriorates over a few years [28-30]. An alternative approach would be to use a therapy or combination of therapies early in the course of T2DM that improve beta cell function and ameliorate insulin resistance [2]. TZDs reduce insulin resistance by modulating the activity of the nuclear receptor PPAR gamma [31]. Activation of these receptors imparts changes in genes that govern insulin signal transduction but such agonist use also improves pancreatic beta cell function in T2DM subjects [32,33]. Bromocriptine-QR has been shown to reduce postprandial hyperglycemia without raising insulin levels in T2DM subjects and to enhance tissue sensitivity to insulin [16,17]. The current findings suggest that the combination of a TZD (with or without another OAA) plus bromocriptine-QR may be an effective strategy of establishing long-lasting improvements in glycemic control in patients with T2DM. In light of the recent FDA and European Medicines Agency actions to either severely restrict or prohibit, respectively, the use of rosiglitazone in T2DM patients due to potential risk of untoward cardiovascular events, these considerations respecting the potential benefits of combination TZD-bromocriptine-QR therapy are directed towards the TZD, pioglitazone.

The biological mechanism(s) by which bromocriptine-QR produced these nearly year-long effects on A1C level in subjects in poor glycemic control on TZDs (baseline A1C: 8.3) and late in the disease process (average duration of T2DM: 8.5 years at baseline) is (are) unknown. Although, the specific effect of combined TZD-bromocriptine-QR therapy on fasting versus postprandial glucose metabolism was not investigated, the placebo-adjusted decline in fasting plasma glucose concentration (-20.5 mg/dl) clearly cannot explain the decrement in A1C (-0.91) among bromocriptine-QR treated subjects. Given the inherently different modes of action of these agents on beta cell function and insulin sensitivity [6-15,34,35] their potential synergistic effects on glycemic control (via impacting fasting and postprandial hyperglycemia) are all plausible and further research is needed to delineate the biochemical/physiological nature of these additive benefits. From a theoretical standpoint, combination therapy early in the progression of T2DM with a TZD that augments beta cell function [6,7] plus bromocriptine-QR that improves postprandial glucose metabolism, apparently by improving insulin sensitivity [16,17] may offer a means of producing long lasting improvements in postprandial glycemic control.

In the Cycloset Safety Trial, only fasting glucose levels and A1C levels were obtained as glycemic indicators. Previous studies with bromocriptine-QR have clearly demonstrated that morning administration of bromocriptine-QR produces significant improvements in post prandial glucose levels without raising insulin levels [43]. A therapeutic approach that reduces postprandial hyperglycemia may offer unique benefits to the treatment of T2DM. Elevation of postprandial glucose is independently associated with increased risk for cardiovascular events [36-38] and microvascular complications [39]. Targeting post-prandial hyperglycemia also appears to offer advantages over focusing solely on fasting hyperglycemia. In a meta-analysis, Hanefeld et al. [40] reported that use of an α-glucosidase inhibitor which primarily reduces postprandial glucose among participants with T2DM was associated with reductions in cardiovascular events. Additionally, in the Cycloset Safety Trial, patients randomized to bromocriptine-QR vs. standard of care experienced a significant 40% relative risk reduction (hazard ratio 0.60; 95% confidence interval 0.37-0.96) in the pre-specified, composite cardiovascular endpoint point with fewer subjects experiencing a CVD event over one year (1.8% vs. 3.2%, respectively) [18]. In a secondary prevention trial (PROactive), pioglitazone also has been shown to reduce cardiovascular events [41]. Therefore, the combination of these two insulin sensitizers that have different modes of action, exhibit a positive effect on postprandial hyperglycemia [16,42] and other cardiovascular risk factors such as postprandial dyslipidemia and inflammation [10,16,17] and reduce cardiovascular events deserves further exploration in larger randomized trials.

The risk of hypoglycemia is low with the combination of a TZD and bromocriptine-QR because neither agent stimulates insulin secretion. Among participants taking a TZD, the occurrence of hypoglycemia was reported as mild and likely attributable to other drugs known to be associated with increased risk for hypoglycemia such as sulfonylurea therapy. Nausea was the most common adverse event reported among participants receiving bromocriptine-QR. There was no increase in weight when bromocriptine-QR was added to participants failing a TZD. Additional studies are warranted to assess if the combination of bromocriptine-QR plus a TZD would minimize the weight gain commonly observed with TZDs [10].

It is important to point out the limitations of the present study. First, the analysis is limited by the relatively small number of participants on TZD therapy (495 out of 3070), in large part due to the fact that the majority of participants in the Cycloset Safety Trial were being treated with metformin and/or a sulfonylurea. Second, the current analysis required adjustments for covariates to fully observe the reported effect of the addition of bromocriptine-QR to participants failing a TZD. Third, the majority (90%) of the subjects in this analysis were being treated at baseline with another OAA in addition to a TZD, so the true relative contributions and nature of the TZDs' and other OAAs' actions upon the mechanistic interactions with bromocriptine-QR to provide the results obtained and described herein cannot be assessed. Finally, a greater proportion of subjects discontinued treatment for reasons other than adverse events with bromocriptine-QR as compared to placebo. However, strengths of this study include that this study is more representative of a real world clinical setting and the unadjusted analysis demonstrates a statistically and clinically significant reduction in A1C among participants taking bromocriptine-QR compared to their usual care after one year of therapy. Additionally, even among subjects with baseline A1C <7.5, those treated with bromocriptine-QR were nearly 3 times more likely to met the ADA recommended A1C of ≤7.0 after 52 weeks. To our knowledge this the first study of its size to assess the added benefit of maintaining ideal glycemic control among patients that on average were well controlled. Additional studies will need to be conducted to confirm whether or not the addition of bromocriptine earlier in the disease course or among subjects already at an A1C of 7.0 or less would result in a greater continued success of maintaining optimal control as compared to current standard practice. Future studies should also investigate whether a lower dose of pioglitazone and bromocriptine-QR therapies used in combination, (and possibly without other OAA on board), would result in prolonged glycemic control while minimizing common side effects such as nausea with bromocriptine-QR and edema and weight gain associated with TZDs.

Conclusions

When administered to patients taking a TZD with or without another OAA agent, bromocriptine-QR significantly improved glycemic control which persisted over one year of treatment. This combination was not associated with increased risk for peripheral edema or weight gain which is common among those treated with TZDs. Evaluation of the relative impact of this combination therapy on fasting and post-prandial glucose warrants further investigation to define the mechanism of action of combination therapy of bromocriptine-QR and a TZD on the physiologic defects responsible for T2DM. The findings of this study support a rationale to pursue additional investigations to evaluate the long term benefits of combination bromocriptine-QR/TZD therapy when initiated early-on in the progression of T2DM.

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