Statistical Analysis Plan
(SAP)

The Effect of Adjunctive Exenatide Treatment on Psychopathology, Cognition and Metabolism in Patients with Schizophrenia

PI: Xiaoduo Fan, MD, MPH

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Participants

Adult outpatients with schizophrenia or schizoaffective disorder were recruited from the UMass Memorial Healthcare System an in Central Massachusetts. Psychiatric diagnosis was determined using the Structured Clinical Interview for DSM-IV (SCID). Other inclusion criteria included: 1) age 18-65 years; 2) stable dose of the current antipsychotic drug for at least one month; 3) well established compliance with outpatient treatment per treating clinician's judgment; 4) able to complete the cognitive assessment battery (must be English speaking); 5) female subjects will be eligible to participate in the study if they are of non-childbearing potential or of child-bearing potential and willing to practice appropriate birth control methods during the study. Exclusion criteria were: 1) inability to provide informed consent, or for individuals with a legal guardian, inability to provide assent or a lack of informed consent from the legal guardian; 2) current substance abuse; 3) Subjects who are not on a stable dose of an antipsychotic medication for at least a month prior to enrollment; 4) psychiatrically unstable per treating clinician's judgment; 5) Uncontrolled medical condition including uncontrolled hypertension, diabetes, seizure disorder, severe cardiovascular, cerebrovascular, pulmonary, thyroid diseases, and gastroparesis; 6) history of ketoacidosis; 7) currently taking insulin; 8) currently taking meglitinides (repaglinide and nateglinide); 9) currently on immunosuppressant medication regularly including oral steroids; topical and inhalant steroids are allowed; 10) currently on sulfonylurea drugs (e.g. glyburide); 11) current, active chronic infection (including tuberculosis, HIV and hepatitis), malignancy, organ transplantation, blood dyscrasia, central nervous system demyelinating disorder, and any other known autoimmune or inflammatory condition; 12) pregnant or breastfeeding; 13) prisoners; 14) estimated glomerular filtration rate (eGFR) < 35 ml/min. The study was approved by the institutional review board of the University of Massachusetts Medical School and followed the Good Clinical Practice guideline.

Procedures

Baseline visit: Eligible subjects came to the clinic for the baseline visit. Fasting blood samples for glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, high sensitivity C-reactive protein (hsCRP), and tumor necrosis factor α (TNF-α) were obtained. The subject completed the clinical symptoms assessment, the extrapyramidal symptoms (EPS) assessment, and vital signs. Then the subject received the study medication (either exenatide 2mg or placebo weekly injection). The randomization was based on a double-blinded 1:1 ratio using permuted block with randomly varying block size.

Follow-up visits (week 1-24): Subjects came to the clinic weekly to receive the study medication injection; possible side effects were assessed weekly. At week 6, 12, 18, 24 visits, vital signs, the clinical symptoms assessment and the EPS assessment were repeated; fasting blood samples for glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, hsCRP, and TNF-α were obtained.

Clinical symptoms assessment: The clinical symptoms assessment included: The Scale for Assessment of Negative Symptoms (SANS), the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression Scale (CGI), the Calgary Depression Scale for Schizophrenia (CDSS), the Heinrichs Carpenter Quality of Life Scale (QLS), the Instrumental

Activities of Daily Living Scale (IADL), and the MATRICS Consensus Cognitive Battery (MCCB).

EPS assessment: The EPS scales included: the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS).

Bioassay: Routine blood tests (glucose, insulin, HbA1c, lipid profile, comprehensive metabolic profile, CBC, hsCRP) were performed at the UMass Core Lab. Insulin immunometric assays were performed using an Immulite Analyzer (Diagnostic Product Corporation, Los Angeles, CA) with an intra-assay coefficient of variation of 4.2–7.6%. Fasting plasma glucose was measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, CA). Glucose assays were run in duplicate, and the intra-assay coefficient of variation ranged from 2 to 3%. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: [fasting serum insulin concentration (μIU/mL) × fasting plasma glucose concentration (mmol/L)]/22.5. Hemoglobin A1C (HbA1c) was measured with high performance liquid chromatography using an automated analyzer (normal range 4.5–6.5%) (SmithKline, Van Nuys, CA). Fasting total plasma cholesterol and triglyceride levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) with dextran sulfate magnesium. LDL levels were determined by the direct LDL reagents (Roche Diagnostics, Indianapolis, IN). Plasma levels of IL-6 and TNF-α were measured by a commercially available enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA). Serum levels of hsCRP were measured via a high-sensitivity latexenhanced immunonephelometric assay on a BN II analyzer.

Statistical analysis: Statistical analysis was performed using SPSS (version 24.0, IBM Corp, Armonk, NY, USA). Descriptive statistics were performed to summarize demographic and clinical characteristics of the study sample. Group comparisons were performed using independent samples t test for continuous variables and the Fisher exact test or Chi-square test for categorical variables. The outcome measures were repeated at different time points. Therefore, analysis of repeated measures using mixed models was performed to compare the change over time in outcome measures between the two treatment groups while controlling for potential confounding variables. The mixed model approach does not require subjects to have the same number of study visits or measurements and uses all available data instead of eliminating subjects with missing data, resulting in unbiased estimates of the model parameters when data are missing at random. Further, for those who completed 24-week treatment, analysis of covariance (ANCOVA) was used to compare change scores from baseline to week 24 between the two treatment groups controlling for potential confounding variables. For all analyses, a P value less than 0.05 (two-tailed) was used for statistical significance.