A Controlled Trial of Losartan in Posttraumatic Stress Disorder

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STUDY PROTOCOL

Study Design

The trial was conducted between 01AUG 2016 and 25FEB 2020 at 6 clinical sites: five University academic medical sites and one University active-duty military hospital. The trial consisted of ten-week, randomized, double-blind, placebo-controlled administration of losartan or placebo. Eligible participants were randomized in a 1:1 ratio based on a randomly permuted block design stratified by site. Participants were prescribed 25 mg of active drug or placebo at Week 0 and then flexibly uptitrated (as tolerated) to 50 mg by Week 2, 75 mg by Week 4, and then 100 mg at Week 6. If significant side effects were encountered, the dosage could be held or reduced to a minimum of 25 mg and held stable at Week 6. Participants unable to tolerate the 25 mg dose were withdrawn from the study.

Losartan and placebo were prescribed as identical capsules, with the losartan overencapsulated. Randomization lists were prepared by the biostatistics analytical team (led by SJ) and distributed to research pharmacies at the sites who dispensed the drug. Only the biostatistics team had access to the treatment assignment codes.

Study Participants

Potential subjects participated in informed consent procedures approved by Institutional Review Boards for each performance site and the Department of Defense Human Research Protection Office (HRPO). A Data Safety Monitoring Board (DSMB) oversaw safety and progress of the study. To be included in the trial, veteran or civilian women and men, aged 18-70 years were required to meet past-month criteria for posttraumatic stress disorder (PTSD) according to DSM-5. Participants were required to have a CAPS-5 score of $\geq$ 25 at screening in order to enter the trial.

Exclusion criteria were: 1) current, imminent risk of suicide (as assessed by the C-SSRS (23)), 2) active psychosis, 3) moderate or severe DSM-5 alcohol or other substance use disorder in the past 3 months, 4) unable to attend regular appointments, 5) prior intolerance of or allergy to losartan or other ARBs, 6) medical illness likely to result in imminent hospitalization or for which treatments are contraindicated (based on lab results, medical history and physical exam) (e.g., systolic blood pressure < 90 mm Hg), 7) serious cognitive impairment (as evidenced by cognitive impairment felt likely to interfere with the ability to participate meaningfully in the

study); traumatic brain injury was not excluded unless there was serious cognitive impairment, 8) concurrent ACE Inhibitors or ARBs, 9) concurrent antidepressants or antipsychotics, and 10) currently pregnant or trying to become pregnant, or of childbearing potential and unwilling to use a proven method of birth control. Potential participants were required to be off of all antidepressants for a minimum of 2 weeks (6 weeks for fluoxetine) prior to randomization; only 2 participants had been on SSRIs prior to entering the study. Sleep agents (e.g., trazodone < 200 mg; eszopiclone; zolpidem) were allowed as long as the dose had been stable for at least 2 weeks; 14 patients used p.r.n. sleep aids during the study. Participation in a trauma-focused psychotherapy during the trial was prohibited. Participation in other psychotherapeutic modalities maintained for 3 months before and during the trial was permitted; 2 patients were on long-term supportive therapy during the study.

Study Procedures

All intakes and interview measures were completed by trained study personnel qualified to conduct the intake assessment. CAPS-5 training and certification was conducted (by Frank Weathers PhD) at the start of the study and yearly recalibration assessment reviews took place at each site. At intake, a standardized past and current medical history with review of symptoms (including allergies to losartan, other ARBs, or any other medications) was obtained. The study physician also conducted a screening medical examination that included determination of standing and sitting blood pressure. Blood was drawn for renal and liver function tests, urine for drug screen, and a baseline EKG. If the patient was a woman of childbearing potential a urine pregnancy test was also done.

Study Assessments

Study assessments occured at baseline week (week 0) and weeks 1, 2, 4, 6, 8 and 10. These assessments included interview and self report measures of symptoms and function, as well as evaluation of adverse events and assessment of standing and sitting blood pressure. The primary endpoint was at 10 weeks and the primary outcome measure was the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; (24)), the gold standard in PTSD assessment. The CAPS-5 past-month was administered at intake and the past-week version re-administered at Weeks 0 (baseline), 4, 8 and 10 week endpoint (or earlier endpoint if the subject discontinued early from the study). Key secondary measures were the PTSD Checklist for DSM-5 (PCL-5; (25)) and the Clinical Global Impressions of Improvement Scale (CGI-I; (26)), and the Patient Health Questionnaire-9 (PHQ-9; (27)) for depressive symptoms.

Genotyping and Genetic Analysis

DNA was collected from salivary samples using the Oragene OG-500 salivary DNA collection Kit. DNA from all participants was extracted using Qiagen extraction kits, and quantifed by gel electrophoresis using Quantity One (BioRad, Hercules, CA) and then normalized. Taqman reactions were performed using Taqman SNP Genotyping Assays along with Taqman Genotyping Master Mix (Applied Biosystems Inc., Foster City, CA). rs4311 alleles were discerned using the 7900HT Fast Real-Time PCR system.

STATISTICAL ANALYSIS PLAN

Statistical Methods

The primary outcome (CAPS-5) was analyzed using an MMRM (mixed model repeated measures) approach based on a modified intent-to-treat (mITT) population, defined as randomized subjects who initiated treatment and had both a baseline and at least one post-baseline outcome score during the blinded phase of the study (Week 10). Participants from the mITT population who were included in the MMRM model also required both a baseline and at least one post-baseline CAPS-5 score. The model included as the dependent variable change from baseline in CAPS-5 total score at each post-baseline visit (Weeks 4, 8 and 10). Independent variables in the MMRM model included treatment, visit, treatment-by-visit interaction, and baseline CAPS-5 total. Visit was treated as a categorical variable. Unstructured variance-covariance structure was used. This same analysis was also repeated on the per protocol population, defined as as all eligible subjects for whom the 10-week assessments for the primary analysis were available and who were dispensed at least 50mg of the protocol prescribed medication at the 6-week time point. Descriptive analyses were performed to compare baseline data between treatment groups. Categorical variables were evaluated using Fisher's exact test. Continuous variables were analyzed with Wilcoxon's rank sum test. Safety data were summarized overall and by treatment groups for the blinded and extended phases of the study. Fisher's exact test was used to compare the number of subjects between groups who experienced any adverse events.

The study was a priori powered assuming 10% attrition and an alpha set to 0.05 using a two-sided, two-sample t-test. Based on a sample size of 160 subjects to have an evaluable sample size of 144 (72 per arm), we could detect with 80% power a standardized change score

between the groups of 47%. All analyses are based on the modified intent-to-treat (mITT) sample unless otherwise specified.

Analogous methods to the primary analysis were used for the other continuous secondary outcomes. The categorical secondary outcome, treatment response status, (response defined as a score of 1 [“Much Improved”] or 2 [“Improved”] on the CGI-I) was analyzed using a generalized estimating equation (GEE) model for binary data. The model included the binary responder status at Weeks 1, 2, 4, 6, 8 and 10 as the dependent variable; treatment, visit and the treatment-by-visit interaction as independent variables. Statistical analyses were performed using R version 3.5.2 (http://www.r-project.org).