

An Open Label Safety and Efficacy Trial of Fenofibrate in Persons with SCI

Lay Abstract

Cardiovascular disease-related morbidity in persons with spinal cord injury (SCI) occurs earlier in life, at a greater prevalence than that of the general population, and is the primary cause of death after the first year of injury. During the chronic phase of SCI, a characteristic dyslipidemia emerges, which is characterized by low serum high density lipoprotein cholesterol (HDL-C) concentrations, with values often qualifying to be an independent risk factor for coronary artery disease, and elevations in serum triglycerides (TG). Serum low density lipoprotein cholesterol concentrations in those with SCI are usually similar to those of the general population. The current proposal in persons with SCI aims to determine the safety and efficacy of short-term fenofibrate treatment, an anti-lipid medication whose primary action lowers serum TG and raises serum HDL-C levels.

Scientific Abstract

Although considered a modifiable risk factor for coronary artery disease (CAD) in the general population, the magnitude of physical activity required to promote cardiorespiratory fitness and a clinically meaningful change in blood-derived biomarkers of CAD is not achievable in those with a severe physical disability, such as with immobilizing paralysis from spinal cord injury (SCI). During the chronic phase of SCI, a characteristic dyslipidemia emerges, with mean serum high density lipoprotein cholesterol (HDL-C) concentrations <40 mg/dl, a threshold level for HDL-C that is appreciated to be an independent risk factor for CAD, elevations in triglycerides (TG) to concentrations at, or near, target values for the general population that trigger clinical intervention, and low density lipoprotein cholesterol (LDL-C) concentrations that are within the normal range. It should not be a surprise that cardiovascular disease (CVD)-related morbidity in persons with SCI occurs earlier in life, at a greater prevalence than that of the general population, and is the primary cause of death after the first year of injury. Population-based epidemiological studies are unavailable for clinical guidance because of the relatively low incidence rates for SCI. Clinical target values used to initiate treatment in the general population may be inappropriate in those with SCI because of their unique pathophysiology. In the absence of significant physical activity and lifestyle modifications, it would seem that appropriate pharmaceutical options are needed to properly manage markers of CVD-related risk in persons with SCI. To date, there is limited empirical evidence to support the use of lipid-lowering treatments in persons with SCI.

Fenofibrate is a fibric acid derivate that activates peroxisome proliferator-activated receptor α and lipoprotein lipase, leading to enhanced elimination of TG from plasma. In clinical trials where fenofibrate was used as a monotherapy, serum TG concentrations fell 41-53%, very low-density lipoprotein (VLDL) fell 38-52%, LDL-C decreased 6-20%, and HDL-C improved by as much as 20%. In consideration for the nature of dyslipidemia in persons with

SCI, fenofibrate appears to be an appropriate first-line agent for treatment in this cohort, especially because most of those with SCI have LDL values that are within the clinically acceptable range. In the general population, standard clinical practice for lipid-lowering treatment with fenofibrate monotherapy follows a known and clinically accepted timeline to monitor safety and to determine therapeutic efficacy. It is recommended that, if after 2 months of continuous therapy there are no beneficial changes to the lipoprotein profile, that treatment be discontinued (i.e., non-responders). Similarly, several large clinical trials have demonstrated that the peak therapeutic effects of fenofibrate are observed after 12-16 weeks of treatment (i.e., responders). The proposed study will test the efficacy of administering fenofibrate to persons with SCI, a severely immobilized cohort that does not have established clinical practice guidelines to treat dyslipidemia and appears to have unique considerations that may be hypothesized to call for a more disease-specific approach for care. If successful, the treatment will reduce clinical markers of CVD-related risk by modifying the concentration and number of particles that are known to contribute to incident cardiac events and mortality. It is anticipated that the insight gained from this investigation will provide clinicians with a proof-of-concept for instituting appropriate use of lipid lowering agents to treat the dyslipidemia that has been well described in persons with SCI.

Goals and Objectives

In individuals with spinal cord injury (SCI):

Primary Aim:

1. To determine the efficacy of fenofibrate monotherapy after 2 months of treatment to improve the lipoprotein profile; a successful response will be defined as a 25% reduction in the serum TG concentration at 2 months. This approach will permit the determination of the percent of subjects who show drug efficacy (i.e., responders) versus those who are non-responders after 2 months of treatment, when drug administration will be discontinued if therapeutic efficacy is deemed suboptimal.
2. To determine the efficacy of fenofibrate monotherapy to lower TG concentration at 4 months of treatment, when the peak therapeutic efficacy to drug treatment has been reported to occur. Lipid profiles will be performed in the drug responder and control groups.

Secondary Aim: To describe the effects of fenofibrate monotherapy on lipoprotein particle number and size by nuclear magnetic resonance spectroscopy performed in non-responders and responders at 2 months of treatment, when drug treatment will be discontinued for lack of efficacy to agent. Lipids in responders and control groups will be studied by NMR spectroscopy at 4 months of treatment, which will be at the termination of the proposed treatment period.

Tertiary Aim: To determine the safety of fenofibrate monotherapy. Documentation and description of adverse events will be obtained in subjects who have received drug treatment compared to events occurring in the control group.

Target Population

It is estimated that approximately 100 participants with SCI will be screened to identify 30 eligible and appropriate SCI participants (i.e., 20 treatment, 10 control) who will agree to participate in the study (Screening data from BAU-11-075 will be used to minimize the number of procedures performed, if it is not older than 45 days). To be considered eligible for the study, participants must meet the following eligibility criteria:

Inclusion Criteria:

- (1) Male or female, age 21 to 69;
- (2) Chronic (e.g., duration of injury at least 6 months), stable SCI (regardless of level of neurological lesion);
- (3) American Spinal Injury Association Impairment Scale (AIS) designation of A, B or C; and
- (4) TG concentration ≥ 135 mg/dl (paraplegia) or ≥ 115 mg/dl (tetraplegia).

Exclusion Criteria (These exclusion criteria were carefully chosen to minimize subject risk and/or confounding factors that are known to affect study endpoints):

- (1) Acute illness or infection;
- (2) Reduced kidney function (by glomerular filtration rate (GFR < 60 ml/min) or liver function tests (LFTs ≥ 2.5 times above the upper limit of normal) as determined by test results at screening and any time point of the study;
- (3) Current pharmacological treatment with: HMG-CoA reductase inhibitors (statins), or any other hypolipidemic agent; anti-coagulant therapy; cyclosporine; or any other medications known to effect the TG concentration (i.e., β -blockers, thiazides or estrogen);
- (4) Hypersensitivity to fenofibrate;
- (5) Existing diagnosis of atherosclerosis, congestive heart failure, or recent history of myocardial infarction (i.e., ≤ 12 months);
- (6) Pregnancy or women who may become pregnant during the course of the study, or those who are nursing;
- (7) Diminished mental capacity; and
- (8) Inability or unwillingness of subject to provide informed consent.
- (9) Existing diagnosis of diabetes mellitus, or the results from screening blood tests indicate that diabetes mellitus is present (and perhaps undiagnosed); laboratory thresholds for exclusion will be as follows: HbA1C $\geq 6.5\%$ and fasting plasma glucose is > 126 mg/dl;

(10) Frequent alcohol consumption greater than 1 drink per day (one drink per day defined as $\frac{1}{2}$ ounce of absolute alcohol that is = to one 1.5 ounce of 80 proof alcohol = one 12 ounce can of beer = one 4 ounce glass of wine).

Participant Recruitment

Potential participants will be recruited in accordance with local regulatory guidelines. The study coordinator will use a variety of methods to approach potential participants, including referrals from clinical staff, in-person contact at clinic visits, telephone calls, and placement of IRB approved flyers in authorized locations. For those participants who have previously signed consent document for a prior study and have requested to be contacted for future research studies, these individuals will be contacted for participation in our proposed study. Eligible participants will be enrolled after satisfying study inclusion/exclusion criteria. To offset the level of inconvenience and perceived risk of the study procedures, remuneration in the amount of \$50 will be provided for successful completion of the screening visit, months 1, 2, 3 and follow-up; subjects will receive \$100 for completion of baseline and month 4 visits. Thus a subject who completes all study visits will receive \$450 for participating in the 6 month study. In the event that an individual performs only the screening visit, discontinues from participation, or is withdrawn, they will be provided partial remuneration commensurate with their length of participation.

Methods

The proposed investigation is an open-label, parallel-group intervention and randomized trial to determine the safety and efficacy of fenofibrate monotherapy on the lipoprotein profile in persons with SCI. A screening visit will be performed in up to 100 persons with SCI to identify 30 subjects who have adverse TG concentrations (i.e., paraplegia: ≥ 135 mg/dl; tetraplegia ≥ 115 mg/dl). After a baseline evaluation, a comprehensive medical history review and intake interview will be performed to identify demographic information, current health status, medications and lifestyle habits (i.e., smoking, alcohol consumption, recreational drug use, physical activity habits, diet etc.). Twenty subjects with adverse TG concentrations will be randomized to receive once daily fenofibrate therapy (i.e., 145 mg) for 4 months (dispensed by the research pharmacy of the James J. Peters VA Medical Center) and the remaining 10 subjects with adverse TG concentrations will receive no treatment and will serve as control subjects. All subjects will complete monthly follow-up visits for the study period, which also includes a 1-month post-treatment visit. If after 2 months of continuous fenofibrate treatment a subject does not demonstrate an improvement of $\geq 25\%$ in TG concentration, then he/she will be discontinued from the study drug under appropriate supervision and terminated from the study. For those who respond to fenofibrate treatment, he/she will continue on treatment for an additional 2 months.

The primary study outcome will be to determine the efficacy of treatment on the serum lipoprotein profile (i.e., TG, HDL-C, LDL-C, total cholesterol), and the secondary study

outcome will be the lipoprotein particle number and size by NMR (i.e., HDL, LDL and VLDL subfractions). Liver (enzymes: AST, ALT, GGT) and kidney function (i.e., glomerular filtration rate) tests, and a complete blood count (CBC) with differential will be performed at all study visits, from blood samples, respectively, to monitor subject safety (Table 2). To facilitate our understanding of the relationship between metabolic parameters, body composition and primary study outcome measurements associated with treatment efficacy, a 2 hour oral glucose tolerance test, and a total body dual energy x-ray absorptiometry (DXA) scan will be performed to quantify total body fat mass and fat-free mass at baseline, as well as to determine visceral adipose tissue volume (enCore™ software (Lunar iDXA, platform version 13.6, General Electric Medical Systems, Madison, WI) at baseline and at 4 months. In addition, all subjects who enter the trial as a treatment or control subject will receive dietetic counseling at baseline and at 2 months. Study support staff will perform phone calls twice a month to monitor drug compliance and direct concerns to the study physician during intervals when there may be noncompliance with scheduled study follow-up visits. Thus, the proposed research investigation incorporates and follows best practices for the clinical treatment and utility of fenofibrate monotherapy in persons with dyslipidemia.

Table 2. Table of Procedures

	Screening	Baseline	Treatment				Follow-Up
			Month 1	Month 2	Month 3	Month 4	Post- 1 month
Safety Labs							
Liver and Kidney Function	x	x	x	x	x	x	x
CBC with Differential	x	x	x	x	x	x	x
Primary Study Outcomes							
Lipoprotein Concentrations	x	x	x	x	x	x	x
Lipoprotein Particle Number		x	x	x	x	x	x
Additional Outcomes							
Fasting Insulin, Glucose and A1	x	x	x	x	x	x	x
Oral Glucose Tolerance Test		x				x	
Body Composition Analysis		x				x	
ApoE blood genotyping		x					

Procedures

Safety Labs: Serum blood specimen will be obtained for the determination of the glomerular filtration rate (GFR). If at screening or during the trial, GFR is <60 ml/min, the potential subject will not be eligible to enroll in the study, or if the GFR should fall to <60 ml/min during the trial, the participant will be discontinued from study drug; renal function will be monitored for a period of at least 4 months after identifying a fall in creatinine clearance while on study drug. Liver function tests [i.e., AST, ALT (<35 IU/L), GGT (elevated for respective age and

gender)] and complete blood count with differential (CBC with diff) will be obtained and evaluated for abnormal values. If evidence for abnormal liver function (i.e., 2 standard deviations above the upper limit of normal) or infection (white blood cell >10,000 cells/ml), the subject will either be considered ineligible for the study at the time of screening or discontinued from study drug under appropriate supervision and monitored for a period of at least 4 months. These specimens will be processed by a commercial laboratory at the time of collection (LabCorp). All safety labs will be reviewed by Dr. William A. Bauman (Co-Investigator and study physician). He will be responsible for the oversight of safety monitoring, eligibility and review of all laboratory data from screening and treatment.

Primary Study Outcomes: Venous blood samples will be obtained after an overnight fast (minimum 8 hours) for the determination of lipoprotein concentrations (i.e., HDL-C, LDL-C, VLDL-C, TG and total cholesterol) and lipoprotein particle number and size (i.e., mean size of HDL, LDL and VLDL particle; the number of HDL, LDL and VLDL for the respective sub-fraction of small, medium and large particles). Lipoprotein concentrations will be processed by a commercial laboratory at the time of collection (LabCorp); lipoprotein particle number and size will be performed as a fee-for-service by Liposcience, Inc (Raleigh, NC, USA).

Additional Outcomes: To assist in the stratification of interventional outcomes, all participants who enter the study intervention (i.e., receive drug or serve as control), will provide a blood sample at the beginning of the treatment period so that their apolipoprotein E (ApoE) genotype can be determined by a commercial laboratory as a fee-for-service procedure (LabCorp). Venous blood samples will be obtained after an overnight fast (minimum 8 hours) for the determination of fasting plasma insulin level and serum glucose concentration at each study visit once the trial begins. For the oral glucose tolerance test, the participant will drink a glucose containing solution (i.e., 75 grams) over a 2-minute period. Venous blood will be drawn from a catheter at time 0 (same blood sample just described) and 120 minutes later to determine plasma glucose and insulin levels. These outcomes will be monitored for changes in glucose tolerance and insulin sensitivity that may be associated with fenofibrate treatment. The Core Laboratory of the Center of Excellence for the Medical Consequences of SCI will perform the glucose analyses (YSI 2300 STAT Plus, YSI Life Sciences, Yellow Springs, OH) and insulin assay by batch processing in duplicate by radioimmunoassay using techniques previously developed by our laboratory.⁵⁸ For body composition analysis, subjects will be transferred from their wheelchair to a semi-padded scanner bed, where a DXA total body scan will be performed. To determine fat mass and fat-free mass, the scan will expose subjects to a very low dose of radiation (i.e., approximately 1/5th of the radiation for a standard chest x-ray). The scan will take no more than 20 minutes to be performed and will only be performed twice during the study (Table 2). Skinfold and Girth Circumference Measurements: a soft measuring tape will be used to measure various circumferences and lengths of each subject's body, and a

set of skin calipers will be used to measure skin folds specifically located on the subject's arms, legs, back, and trunk. The total time of this procedure will not exceed 10 minutes.

Potential Risks

The health risks associated with this research study are minimal in nature. As with any investigational study, there may be adverse events or side effects that are currently unknown. In the case of a serious adverse event during the test, hospital emergency personnel will be summoned over telephone by study personnel. The following list contains potential risks/and or discomfort related to study procedures:

-Fenofibrate: Common side effects for treatment include abdominal pain, skin rash, and nausea. Less common side effects include gas, bloating, change in bowel frequency and stool color. As mentioned previously participants are at risk to develop elevated and/or abnormal liver and kidney function from taking Fenofibrate. If abnormal levels become evident as indicated by safety monitoring labs taken at each time point, the subject will be discontinued from study drug and monitored on a monthly basis for up to four months or until liver function returns to normal. In addition, if the subject develops elevated and/or abnormal liver function results, they may experience the following: yellowing of eyes/skin, dark urine, pruritis, swelling, and headache.

-Blood draw/catheter placement: The subject may experience the feeling of being lightheaded, dizzy, blurry eyesight, nausea and/or syncope during the needle/catheter insertion. There is also the potential risk of developing a bruise or infection at the site of skin puncture.

-Oral glucose tolerance test: In addition to the listed risks for blood draw/catheter placement, the ingestion of a large volume of glucose may cause some individuals to experience nausea.

-Dual energy x-ray absorptiometry scans: To complete the scan, participants will be asked to transfer from their wheelchair to the scanning bed. This will be completed independently or with assistance from an overhead patient lift. The scan will take approximately 15 minutes to complete during which the subject will be asked not to move. Each dual energy x-ray absorptiometry scan will expose the subject to 8.62 μ Sv of radiation (i.e., equivalent to 1/5 of an average chest x-ray), thus each subject will receive 17.24 μ Sv for the two scans.

Statistical Analyses

Separate analysis of variance (ANOVA) will be performed to identify group differences (i.e., control, treatment) for baseline demographic data [e.g., age, height, weight, BMI, duration of injury (DOI)]. Pearson chi-square tests will be performed to identify differences for the number of enrolled participants in each group based on gender (e.g., male, female), injury level (e.g., paraplegia, tetraplegia), AIS level (e.g., A, B, C), and ethnicity (e.g., African American, White, Hispanic). Separate 2 (group: treatment, control) X 3 (visit: baseline, Mo2, Mo4) mixed-model repeated measures ANOVA (RMANOVA) will be performed to determine if differences were present for serum lipoprotein profile [e.g., HDL-C, LDL-C, VLDL-C, TG, TC], glucose, insulin, and the TG/HDL-C, LDL-C/HDL-C and TC/HDL-C ratios. Separate

factorial ANOVA will be performed to identify the presence of group differences in the percent change from baseline to 2 and 4 months, respectively in the serum TG, HDL-C, and LDL-C. The nature of significant group or time main effects will be explored with Tukey *post hoc* tests. Although not part of the primary analysis, results from the venous blood samples at months 1 and 3 visits will be provided. Statistical analyses will be completed using IBM SPSS Statistics 25 (IBM, Armonk, NY) and figures will be created with GraphPad Prism (version 8.0 for Windows, GraphPad Software, San Diego, CA). An *a priori* level of significance was set at $p \leq 0.05$.