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TITLE: Increasing Bone Mass and Bone Strength in Individuals with Chronic Spinal Cord Injury: Maximizing Response to Therapy

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall objective of this research is to determine the optimal approach to enhancing and maintaining bone mass and bone strength in people with chronic SCI. Our previous research showed that teriparatide treatment can result in an increase in bone mass in people with SCI. We hypothesize that initiating a subsequent one year of treatment with alendronate will result in a further increase in bone mass and bone strength. In this study, participants terminating 2 years of teriparatide therapy are treated with open-label oral alendronate for one year. All participants are evaluated with bone imaging (DXA and CT scanning) and serum bone markers at 6 monthly intervals during the course of the study. Correlation of BMD and bone strength with fracture prevalence and incidence will also be undertaken in order to define a fracture threshold. 17 participants have been entered into this study; all have completed one year of treatment. All data have been recorded and entered. Analysis is on-going. Bone strength testing has been initiated and data collection is on-going.

15. SUBJECT TERMS
Spinal cord injury, bone mass, bone strength, osteoporosis, alendronate, teriparatide

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INTRODUCTION:

Parathyroid hormone (PTH) is a potent bone-building hormone, and teriparatide (a biologic agent containing the amino-terminal 34 amino acids of human PTH) is the only anabolic agent approved by the FDA for the treatment of osteoporosis and the prevention of fractures. Although the optimal duration of teriparatide therapy for the treatment of osteoporosis is not known, discontinuation of teriparatide treatment has been shown to be followed by rapid decreases in bone mass and bone strength. These reductions in bone mass can be prevented by initiating treatment with a bone anti-resorptive agent once teriparatide is discontinued. The current study takes advantage of an on-going factorial designed clinical trial of people with spinal cord injury (SCI) and low bone mass who have been treated with a combination of teriparatide and lower extremity loading (based on mechanical vibration) for either one or two years. The goal of the current study is to determine the effect of an additional year of treatment with the anti-resorptive agent, alendronate, a widely-used bisphosphonate, in this setting. The hypothesis being tested is that alendronate therapy will prevent the bone loss that occurs when teriparatide is stopped and possibly result in a further increase in bone mass and bone strength. In this study, participants completing the second year of the parent study with teriparatide will be administered open-label oral alendronate 70mg weekly for 12 months. DXA imaging, CT imaging and bone markers will be obtained at baseline, 6 months and 12 months to ascertain effects on bone mass, bone strength and bone metabolic processes. In addition, a parallel study using cadaveric bone specimens will be undertaken to evaluate and define parameters relating to bone strength to support a finite element analysis which will be used to define a fracture threshold which can be used to identify individuals who may be at high risk of bone failure and clinical fracture.

KEYWORDS: spinal cord injury, bone mass, bone strength, osteoporosis, alendronate, teriparatide

OVERALL PROJECT SUMMARY:

All objectives outlined in the Statement of Work to be completed during the first year for Aim 1 and Aim 2 have been completed. All regulatory approvals have been obtained and maintained. Enrollment and treatment of participants (Specific Aims 1 and 2, Major Task 2) have been completed, with 17 participants having been entered into the study. The database has been locked and data analysis is now complete (Specific Aims 1 and 2, Major Task 3). Safety was continually monitored by collection of adverse events and their evaluation at a regularly held data safety monitoring committee meeting. No safety concerns have been identified and no changes in the study proposed.

Specific Aim 3 is focused on the validation of computed tomography based finite element models to quantify changes in torsional and compressive strength at the distal femur and proximal tibia, and to subsequently correlate fracture prevalence and incidence after SCI with these measures of strength. The models will be validated using a combined numerical-experimental study using cadaveric materials and mechanical testing. All cadaveric materials have been acquired (n = 28 bones) and mechanical testing fixtures have been fabricated. Mechanical testing has been completed for 5 bones (3 femora, 2 tibiae) and the remaining specimens are being prepared for testing (i.e., removing soft-tissue, potting in polymethylmethacrylate, and imaging using computed tomography). Mechanical testing is estimated to be completed this fall, upon which time model validation will begin.

KEY RESEARCH ACCOMPLISHMENTS:

The database has been locked and preliminary data analysis has been completed. A table with baseline demographics and clinical descriptors (Table 1) and a summary of DXA and bone marker analyses (Table 2) have been included in the appendix.

DXA Results: Our preliminary results demonstrated a significant effect of time for areal bone mass density (aBMD) measured by DXA at the lumbar spine. After 12 months of treatment with alendronate, spine aBMD was on average 2.54% greater (95% CI: 0.17 to 4.90) and showed a significant interaction of time by treatment (p=0.037). The difference after one year of exposure was not significant for the hip and femoral neck aBMDs. However, a trend towards an interaction was observed with an average increase of 1.32% (95% CI: -1.10 to 3.37) in the hip. Almost no effect was observed with an increase of 0.54% (95% CI: -2.03 to 3.11) in the femoral neck.
Bone Marker Results: There was a significant interaction of time by treatment for CTX (p= 0.003) and P1NP (p= 0.020). Both saw a downward trend after 12 months of treatment. Compared to baseline, CTX and P1NP had a change of -61.75% and -51.53%, respectively. There was no significant difference from baseline for the BSAP marker (p= 0.362) with a -15.54% change.

CT-derived bone measurements and bone strength: These results are still pending at this time.

CONCLUSION:

Our preliminary results suggest that one year of treatment with alendronate following treatment with teriparatide prevented the decrease in DXA-determined aBMD that typically occurs after cessation of an anabolic intervention such as teriparatide therapy. One year of alendronate therapy demonstrated that increases in bone density gained from teriparatide use were sustained.

Alendronate had a variable effect at skeletal sites in chronic SCI patients. After one year of alendronate treatment, participants experienced a continued significant increase of spine aBMD with a smaller numerical increase in aBMD at the hip. Thus by avoiding further bone loss and gaining new bone, this intervention may have the potential to reduce fracture incidence in people with chronic SCI.

PUBLICATIONS, ABSTRACTS AND PRESENTATIONS:

None.

INVENTIONS, PATENTS AND LICENSES:

None.

REPORTABLE OUTCOMES:

None.

OTHER ACHIEVEMENTS:

None.

REFERENCES:

None.

APPENDICES:

Table 1. Demographics and Clinical Descriptors

Open Label Cohort n	
Participants	17
Age mean ± SD	
Years	43.9 ± 13.2
Gender n (%)	
Male	13 (76)
Female	4 (24)
Ethnicity n (%)	
Non-Hispanic	14 (82)
Hispanic or Latino	3 (18)
Race n (%)	
Caucasian	9 (53)
African American	7 (41)
Asian	1 (6)
Time since Injury mean ± SD	
Years	14.9 ± 9.2
Classification of Injury n (%)	
Cervical	4 (24)
Thoracic	11 (65)
Lumbar	2 (12)
ASIA A	12 (71)
ASIA B	1 (6)
ASIA C	4 (24)
Motor Complete	13 (76)
Motor Incomplete	4 (24)

Table 2. Mean percent difference (±95% confidence intervals) in measurements relative to baseline after one year of alendronate treatment. Significant values are bolded.

	Measure	Mean Difference (95% CI)	p-value
Bone Markers	CTX	-61.75 (-99.85 to -23.66)	**0.003**
	P1NP	-51.53 (-93.79 to -9.27)	**0.020**
	BSAP	-15.54 (-50.62 to 19.55)	0.362
DXA (aBMD)	Spine	2.54 (0.17 to 4.90)	**0.037**
	Hip	1.32 (-1.10 to 3.75)	0.266
	FN	0.54 (-2.03 to 3.11)	0.662

Increasing Bone Mass and Bone Strength in Individuals with Chronic Spinal Cord Injury: Maximizing Response to Therapy

Proposal Log Number BA150039; Award # W81XWH-16-1-0763; HRPO Log A-19839

PI: Dr. Thomas J. Schnitzer **Org:** Northwestern University Feinberg School of Medicine **Award Amount: $489,901**

Study/Product Aims

- Determine effect of treatment with alendronate on bone mass after teriparatide in people with SCI and bone loss.
- Determine effect of treatment with alendronate on bone strength after teriparatide in people with SCI and bone loss.
- Quantify changes in torsional and compressive strength at the distal femur and proximal tibia and correlate with fracture prevalence and incidence.

Approach

This study has two parts: 1) An open-label extension study with alendronate in individuals who had received teriparatide for low bone mass, with DXA BMD, CT BMD and bone markers as outcomes and 2) Analysis of data from that study including finite element modeling to quantify changes in bone mass and bone strength and then correlate these with fracture prevalence in SCI.

IRB approval received at all sites. Enrollment completed. Seventeen subjects have completed the study. Data collected and analyzed. Bone strength modeling and analyses continuing.

Timeline and Cost

Activities CY	16	17	18	19
Study Start-Up Activities				
Data Collection and Entry				
Analysis of Clinical Data				
FEA modeling and analysis				
Estimated Budget ($K)	**$96K**	**$315K**	**$78K**	**$0K**

completed | original projected | current projection

Goals/Milestones

CY16 Goals – Begin study start-up

- Obtain regulatory approval at all sites

CY17 Goals – Complete all data collection.

- Initiate and undertake data analysis for alendronate study
- Obtain CT BMD data parameters, serum bone marker values

CY18 Goal – Completion of all elements of clinical study.

- Complete data analysis and submit publication for alendronate study
- Continue modeling and analysis for bone strength correlations

CY19 Goal

- Complete modeling and analysis for bone strength correlations
- Final study report

Comments/Challenges/Issues/Concerns

- On track with Part 1 of the study; Part 2 has been delayed due to time to obtain regulatory approvals and procurement of materials

Budget Expenditure to Date:

Projected Expenditure: $489,901

Actual Expenditure: $473,561 (subcontract encumbered)

Updated: 10October2018