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14. ABSTRACT

Over 27 million Americans are currently diagnosed with osteoarthritis (OA), and OA is our nation's leading cause of pain and disability. Medically linked retirement caused by musculoskeletal disorders such as OA increased nearly 10-fold among active military service members between 2003 to 2009. The rate of OA in military populations is twice as high as that in non-military populations. Neither a disease-modifying OA drug nor a non-surgical cure presently exists. Therefore, it is extremely important to have a drug which mitigates OA disease progression and relieves OA pain, with minimal, if any, adverse effects. The aim of the current project is to determine the therapeutic efficacy of a novel botanical drug using a canine model of post-traumatic OA, a large animal model that replicates the pathology and symptoms of human OA. Successful completion of the proposed studies will provide critical evidence to the Food and Drug Administration for approval for human

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TABLE OF CONTENTS

1. Introduction

Over 27 million Americans are currently diagnosed with osteoarthritis (OA), and OA is our nation's leading cause of pain and disability. Medically linked retirement caused by musculoskeletal disorders such as OA increased nearly 10-fold among active military service members between 2003 to 2009. The rate of OA in military populations is twice as high as that in non-military populations. Neither a disease-modifying OA drug nor a non-surgical cure presently exists. Therefore, it is extremely important to have a drug which mitigates OA disease progression and relieves OA pain, with minimal, if any, adverse effects. The aim of the current project is to determine the therapeutic efficacy of a novel botanical drug using a canine model of post-traumatic OA, a large animal model that replicates the pathology and symptoms of human OA. Successful completion of the proposed studies will provide critical evidence to the Food and Drug Administration for approval for human clinical trials.

2. Keywords

Post-traumatic osteoarthritis, botanical drug, canine osteoarthritis, gait analysis, disease-modifying drug, osteoarthritis pain

3. Accomplishments

Major goals of the project

The major goals of the project remain unchanged from the original proposal:
Specific Aim 1: Determine efficacy of C'-CEO in mitigating OA disease progression
Specific Aim 2: Determine efficacy of C'-CEO in mitigating OA-related pain

The next milestone as listed in the approved Statement of Work is at month 18 – "Surgical induction of OA, daily treatment with C'-CEO or placebo, and euthanasia." The approximate percentage of completion towards the entire project is approximately 95%.

What was accomplished under these goals?

During the second year, we made progress towards the proposed milestones including:

1) Surgical induction of OA, daily treatment with C'-CEO or placebo, and euthanasia
2) Macroscopic and histopathologic evaluation of joint tissues
3) Micro computed tomography of subchondral bone

Skeletally mature canines (female hounds, n=12 total) without pre-existing musculoskeletal abnormalities of the pelvic limbs (determined by radiographic examination) were subjected to the meniscal release model of OA. At 4 weeks after induction of experimental OA canines were treated daily with oral administration of C'-CEO or placebo for 10 weeks (n=6/group). Prior to and every 4 weeks following surgery, OA pain-

related outcome measurements were accessed by kinetic gait analysis. At 10 weeks after treatment, the animals were sacrificed, and the stifle joints were collected for histological analysis.

Surgical induction of OA, daily treatment with C'-CEO or placebo, and euthanasia was completed for n=8 canines. Below are the major findings from the second year.

We carried out microCT analysis of the first batch of dogs from this study. For each individual dog, we calculated average cartilage thickness and cartilage volume (Fig. 1), as well as the subchondral bone properties including average subchondral bone plate thickness trabecular volume, and average trabecular thickness (Fig. 2) of the medial tibial plateau, the compartment commonly affected in the meniscal-release model of OA. Representative images from the microCT analysis are shown in Fig. 3. These data are currently blinded, so we presented each individual dog's operated knee (MR) vs their contralateral control (Ctrl), which was not operated on.

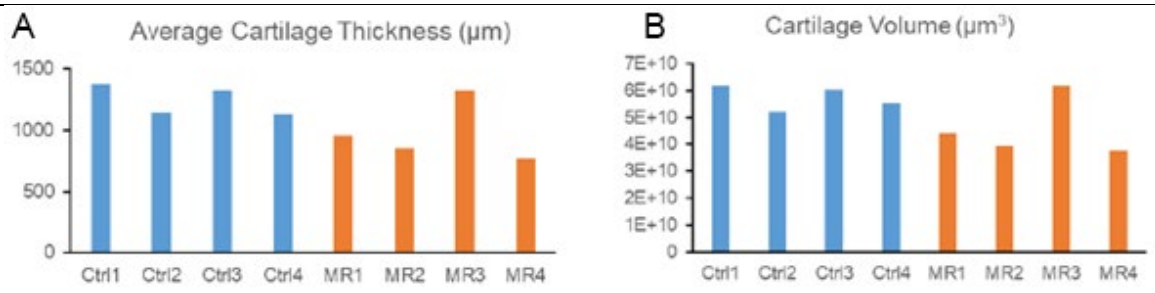

Fig. 1. (A) Average cartilage thickness and **(B)** cartilage volume of dogs subjected to OA-induced surgery (meniscal release, MR) followed with treatment with C'-CEO (drug) or placebo. One of the dog's hind limbs was subject to the meniscal release surgery at week 0. The dogs were treated starting at 4 weeks with C'-CEO or placebo until 14 weeks (n=2 drug; n=2 placebo).

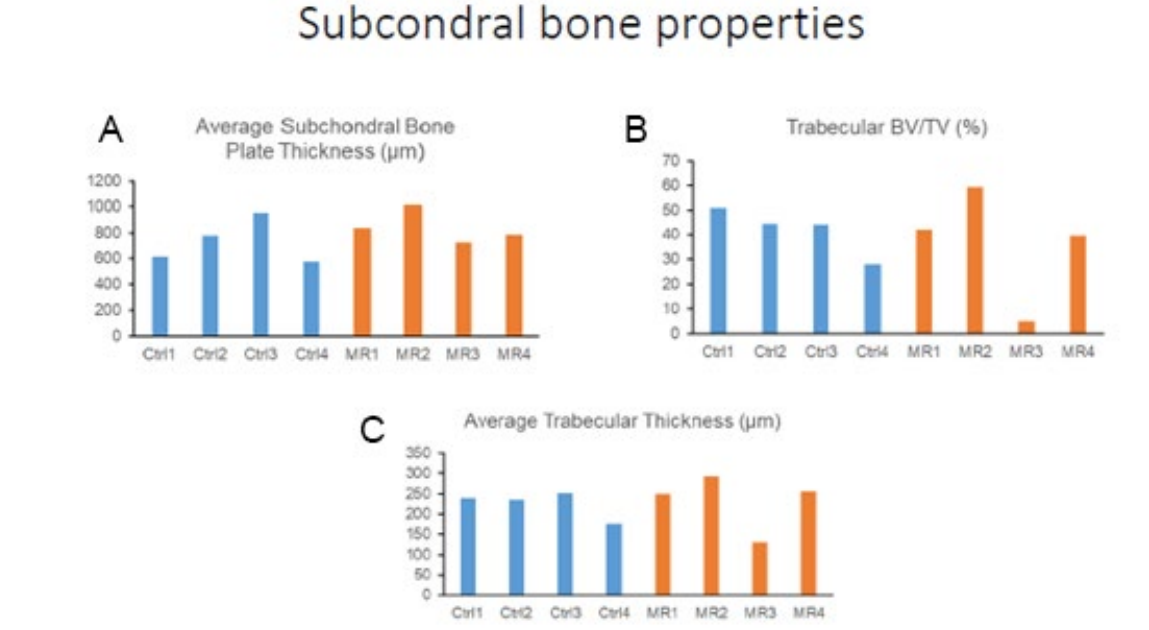

Fig. 2. (A) Average subchondral bone plate thickness, **(B)** trabecular BV/TV and **(C)** average trabecular thickness of dogs subjected to OA-induced surgery (meniscal release, MR) followed with treatment with C'-CEO (drug) or placebo. The dog model used is described in Fig. 1.

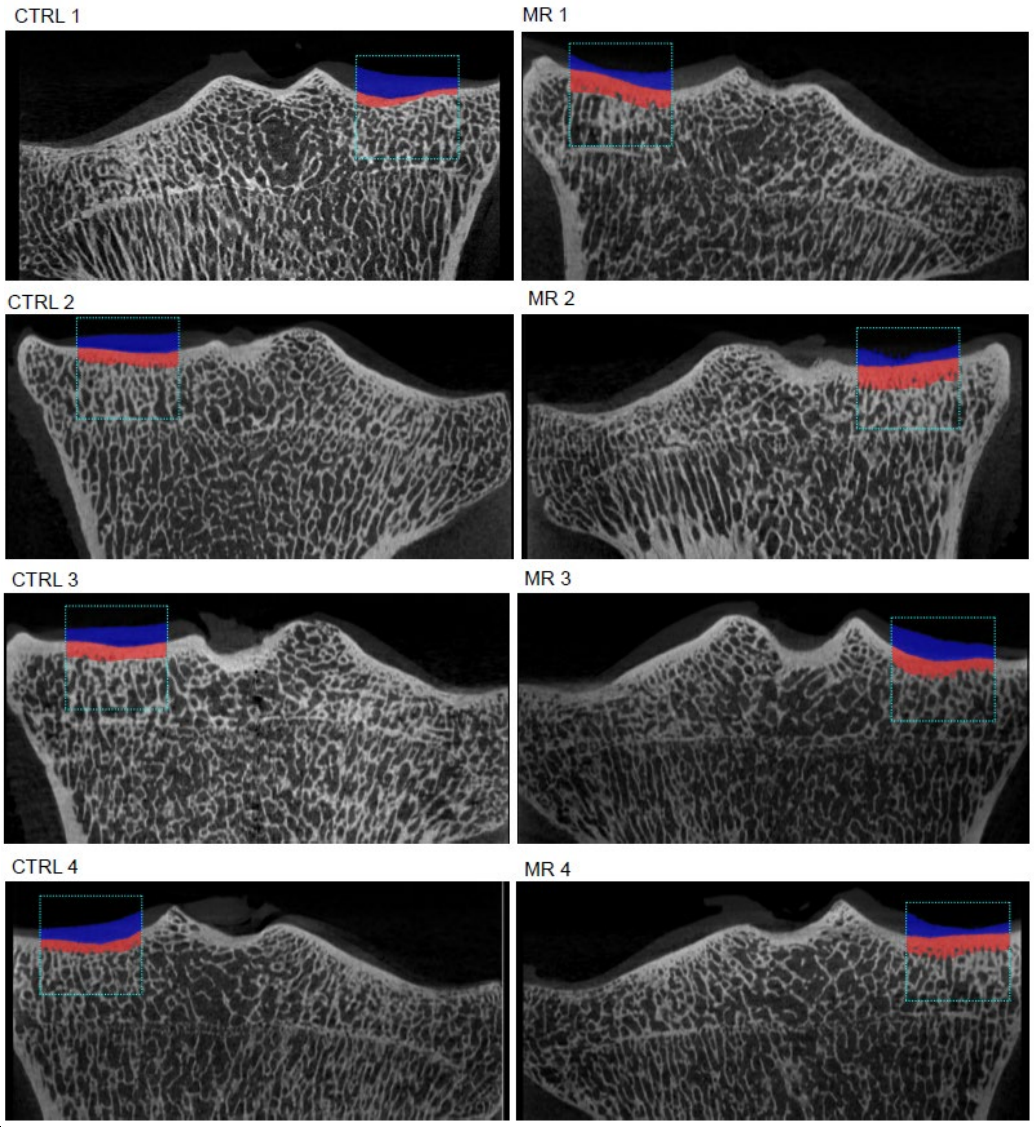

Fig. 3. Representative microCT images of the tibial plateau of each dog. The region-of-interest highlighted. The blue region represents the articular cartilage and the red region represents the subchondral bone. The dog model used is described in Fig. 1.

During the 2nd year, we also carried out gait analysis for the 2nd batch of dogs. The gait analysis for all the animals in the study so far is shown in Fig. 4. In lay terms, these data show how much force the dogs are putting on the ground when they trot. The higher the force measurement, the more the dogs are using the leg, and are probably feeling less pain. Preliminary analysis suggests that the dogs treated with C'-CEO exhibit less OA-related pain and have improved joint function compared to that treated with placebo.

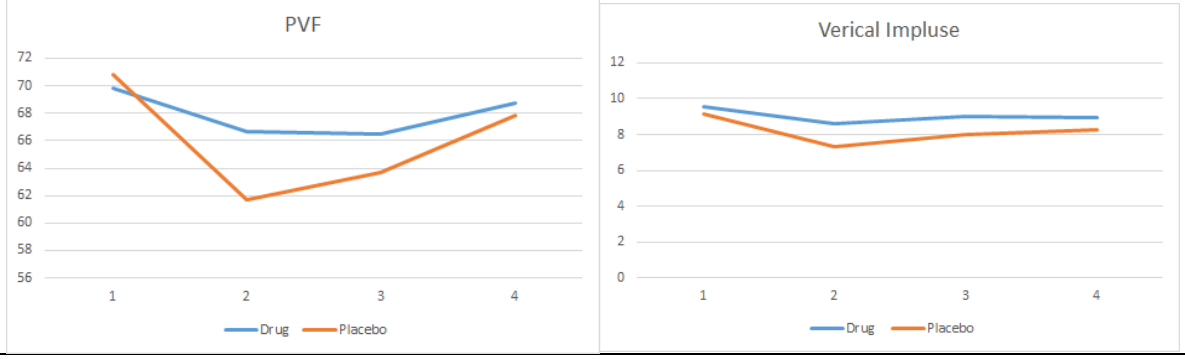

Fig. 4. Gait analysis of dogs subjected to OA-induced surgery (meniscal release, MR) followed with treatment with C'-CEO (drug) or placebo. Gait analysis is taken at baseline (before MR), and at 4, 8, and 14 weeks. Dogs were treated starting at 4 weeks after surgery, and until 14 weeks. n=4/group.

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

During the no-cost extension period, we expect to complete surgical induction of OA, daily treatment with C'-CEO or placebo, and euthanasia, as well as the macroscopic and histopathologic evaluation of joint tissues, and micro computed tomography of subchondral bone.

4. Impact

Nothing to Report.

5. Changes/Problems

A no-cost extension was requested due to delays caused by COVID-19 and the transfer of the grant from Albert Einstein College of Medicine to Ny.TmT.

6. Products

Nothing to Report.

7. Participants & Other Collaborating Organizations

Name	Hui B. Sun, PhD
Project Role	PI
Nearest person month worked	1
Contribution to Project	Dr. Sun coordinated macroscopic evaluation and micro computed tomography of subchondral bone. Dr. Sun worked with the research team at the University of Georgia for the sacrifice of the 2nd group of canines.

Name	Steven Budsberg, DVM, MS, DACVS
Project Role	Co-I
Nearest person month worked	1
Contribution to Project	Dr. Budsberg carried out the meniscal release surgeries and oversaw the gait analysis and drug/placebo administration. Dr. Budsberg also coordinated the sacrifice and tissue harvest from the 2nd group of canines and carried out the macroscopic evaluation of the stifle joints.

Name	Meghan Norton
Project Role	Research Technician
Nearest person month worked	9
Contribution to Project	Ms. Norton assisted with the canine surgeries, fed the dogs daily with drug/placebo, carried out the gait analysis, and assisted with the sacrifice and tissue harvest from the first group of canines.

8. Special Reporting Requirements

Updated Quad Chart attached.

9. Appendices

N/A