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Pilot study of a myostatin antagonist in dogs with cardiac cachexia

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Abstract *Objectives:* Cardiac cachexia, a loss of lean body mass caused by heart disease, often accompanies congestive heart failure (CHF). Blocking myostatin, which is a protein that inhibits muscle growth, appears to greatly enhance muscle size and strength in rodent models and human clinical trials. The objective of this study was to evaluate a dog-specific myostatin antagonist (CAP-031) in a pilot study to test its safety and efficacy in dogs with CHF and cardiac cachexia.
Animals: Dogs with CHF and cardiac cachexia.
Methods: Eligible dogs received four weekly subcutaneous injections of CAP-031. Endpoints were body weight, body condition score (BCS, on a 1—9 scale), muscle condition score (MCS, on a five-point scale, where 0 = no muscle loss and 4 = severe muscle loss), appetite, and a quality of life (QOL) score.
Results: Seven dogs with CHF and moderate-to-severe cachexia were enrolled in the study. For the six dogs that completed the study, the median age was 8.8 years (range 6.4—10.6). At baseline, the median body weight was 27.0 kg (range 17.3—62.0), the median BCS was 4 (2—5), and median MCS was 3 (3—4). There were no significant changes in body weight, BCS, appetite, or QOL score. The change in MCS (from a median of 3 at baseline to a median of 2.5 at week 4) was not statistically significant ($p = 0.06$).

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Conclusions: The myostatin antagonist appeared to be well tolerated in most dogs. Earlier identification of cachexia is important, and randomized, controlled trials of myostatin antagonists or other drugs to treat cardiac cachexia are needed.

Abbreviations

ActRIIB	activin receptor type IIB
BCS	body condition score
CHF	congestive heart failure
CM	cardiomyopathy
MCS	muscle condition score
MMVD	myxomatous mitral valve disease
QOL	quality of life

Introduction

Cachexia, a loss of lean body mass, is a common syndrome associated with many different diseases that occur in people, dogs and cats, including congestive heart failure (CHF), chronic kidney disease, and cancer.[1] In CHF, this syndrome is called cardiac cachexia and occurs in up to half of all people and dogs with CHF.[1,2] In people, cachexia negatively affects strength, immune function, wound healing, and is independently associated with poor survival.[1,2] While the complex and redundant mechanisms of cardiac cachexia are becoming better understood, there are still limited treatment methods for this common syndrome. Optimal management of the underlying disease and careful attention to nutrition are very important, but are often insufficient to block or even slow the progression of muscle loss. Because cachexia is estimated to affect more than five million people in the United States alone,[3] and because of its serious clinical implications, there is now extensive research into the prevention and treatment of this syndrome in people. A variety of different mechanisms and targets are being evaluated,[1,2] but one promising area is myostatin antagonism.

Myostatin is a protein that negatively regulates skeletal muscle mass.[4] Factors that decrease myostatin concentrations (e.g. exercise, myostatin mutations) result in increased muscle size, while factors that increase myostatin concentrations (e.g. tumor necrosis factor, angiotensin II, CHF) contribute to muscle loss.[4] Because myostatin has been shown to be increased in many, but not all, induced animal models and people with CHF,[5–8] myostatin antagonism is hypothesized to be an effective method of preventing and treating cachexia. Myostatin antagonism has been studied in rodent models of cachexia,[9–11] but large clinical trials in people with cachexia, sarcopenia, or muscular dystrophy have not yet been published. Studies of myostatin antagonism have not been reported, to date, in dogs with cardiac disease or cardiac cachexia.

Myostatin inhibition can be achieved with myostatin antibodies or by blocking the activin receptor type IIB (ActRIIB), which is the primary binding site for myostatin.[4] A decoy ActRIIB receptor has been developed and studied in rodent models of aging, CHF, and cancer,[12,13] as well as in a phase 2 clinical trial for boys with Duchenne muscular dystrophy (although the phase 2 clinical trial was subsequently suspended).[14] To be used in different species, the IgG Fc region can be replaced so that the molecule is species specific. One company developed a decoy ActRIIB receptor with a human IgG Fc region for human use (ACE-031), a rodent IgG Fc region for use in rats (RAP-031), and a canine IgG Fc region for use in dogs (CAP-031).[13]

In the present study, it was hypothesized that myostatin antagonism in dogs with cardiac cachexia would be beneficial by increasing muscle mass, or at least preventing further muscle loss. While previously evaluated in dogs with muscular dystrophy and judged to be well tolerated and effective (Ravi Kumar, personal communication), this molecule has not been assessed in dogs with naturally occurring cardiac cachexia. Therefore, the purpose of this pilot study was to evaluate the safety and efficacy of a canine-specific myostatin antagonist in dogs with cardiac cachexia.

Animals, materials and methods

To be eligible for this pilot study, dogs had to have CHF secondary to myxomatous mitral valve disease (MMVD), cardiomyopathy (CM), or congenital cardiac disease. In addition, dogs had to have marked to severe muscle loss. Muscle condition score (MCS) was assessed on a subjective five-point scale, where 0 = no muscle loss, 1 = mild muscle