

Evidence for partial pharmaceutical reversal of the cancer anorexia–cachexia syndrome: the case of anamorelin

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Abstract

A major component of the cancer anorexia–cachexia syndrome is a decline in food intake. Up until now none of the drugs that improve appetite also improve skeletal muscle. Recent studies have suggested that the oral ghrelin-analog, anamorelin, increased food intake and muscle mass. Unfortunately, it does not increase muscle power. Its regulatory future is uncertain, although it has important clinical effects.

Loss of muscle and fat mass and anorexia are the key components of the cancer anorexia–cachexia syndrome.¹ This syndrome plays a key role in the end stage ‘suffering’ of persons dying from cancer. While nutritional intervention can reverse some components of this syndrome, it is insufficient to make a major impact on the outcomes in most patients with cancer.^{2,3} This has led to a search for drugs that will increase food intake and muscle mass quality in persons with cancer.^{4,5} While megestrol acetate, dronabinol and corticosteroids increase appetite, they have not been shown to alter muscle mass.⁶ Anabolic steroids increase muscle mass but have no effect on appetite.⁷

Ghrelin, a 28-amino acid hormone, discovered in 1999, is produced from the fundus of the stomach. It increases food intake, growth hormone release and enhances memory.^{8,9} The effects of ghrelin on food intake and growth hormone release are mediated through the nitric oxide-AMP kinase food regulatory system.¹⁰

Anamorelin is a ghrelin receptor agonist that can be administered orally. Recently, two-phase two multicentre studies involving 82 persons treated for 12 weeks have been published.¹¹ Anamorelin increased lean body mass compared with placebo and improved non-dominant handgrip strength. This was correlated with an increase with insulin-like growth factor 1. In addition, anamorelin administration led to an increase in quality of life.

However, the Phase III trials (ROMANA 1 and ROMANO 2) presented at the 2014 European Oncology Congress in Madrid were somewhat less exciting. In these studies, a total of 979 patients with non-small cell lung cancer were studied. In this study, body weight was increased compared with placebo, but there was no improvement in handgrip strength. In addition, anamorelin improved the Functional Assessment of Anorexia Cachexia Treatment scores.

The results are not unsurprising as ghrelin increases muscle mass by increasing growth hormone. Growth hormone increases muscle mass but not muscle strength.¹² It is now well recognized that muscle quality is not directly related to muscle mass.¹³ This has led to the definitions for sarcopenia requiring the older person not only to have a decrease in lean mass but also in a functional measure (either walking speed/distance or handgrip strength).^{14,15}

The question now arises whether or not a drug that improves appetite and muscle mass, but not muscle function, can be approved for the treatment of the cancer/anorexia syndrome. Both megestrol acetate and dronabinol are approved in the USA as appetite stimulants for anorexia in cancer. This precedent suggests that the approval for anamorelin could be for improving appetite. Improving anorexia is a major quality of life issue in the cancer anorexia–cachexia syndrome. And if the aforementioned question is answered in the affirmative, can such an approval be based on secondary

rather than primary endpoints of pivotal trials? Maybe at least one more trial is needed to confirm these clinically important results.

There are some data suggesting that muscle and/or fat loss in persons with cachexia is protective against early mortality.^{16,17} In addition, prevention of weight loss may improve the ability of persons with cancer to tolerate chemotherapy.¹⁸ Obviously, if anamorelin could be shown to clearly support either of these two concepts, it could become a very important often used drug.

For those scientists who are interested in muscle wasting disease,¹⁹ this is an exciting time as a number of drugs with potential positive effects on muscle wasting are under development and are coming closer to possible approval by the European and American Drug Agencies. We hope that the therapeutic developments will not only affect outcomes

in cancer^{20–22} but also in chronic kidney disease and heart failure,^{23,24} stroke,²⁵ COPD,²⁶ and frailty due to aging.^{27,28} From 4 to 6 December 2015 in Paris, we will organize the eighth Cachexia Conference (for details, see www.society-scwd.org), and hope for many participants and more news on many new therapeutic developments, combining effective drugs with good nutrition.

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