

ABSTRACT

BACKGROUND: Cancer cachexia is a catabolic syndrome associated with uncontrolled muscle breakdown. There may be associated fat loss. Occurring in high frequency in advanced cancer, it is an indicator of poor prognosis. Besides weight loss, patients experience a cluster of symptoms including anorexia, early satiety, and weakness. The 3 stages of cachexia include stages of precachexia, cachexia, and refractory cachexia. Refractory cachexia is associated with active catabolism or the presence of factors that make active management of weight loss no longer possible. Patients with refractory cachexia often receive glucocorticoids or megesterol acetate. Glucocorticoid effect is short and responses to megesterol are variable. Anamorelin is a new agent for cancer anorexia-cachexia, with trials completed in advanced lung cancer. Acting as an oral mimetic of ghrelin, it improves appetite and muscle mass. This article reviews the pharmacology, pharmacodynamics, and effect on cancer cachexia.

METHODS: A PubMed search was done using the Medical Subject Headings term anamorelin. Articles were selected to provide a pharmacologic characterization of anamorelin.

RESULTS: Anamorelin increases muscle mass in patients with advanced cancer in 2-phase 3 trials.

CONCLUSIONS: Anamorelin improves anorexia-cachexia symptoms in patients with advanced non-small-cell lung cancer.

KEYWORDS: Anorexia, cachexia, ghrelin, anamorelin, handgrip strength

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Introduction

Cancer cachexia is a catabolic syndrome associated with irreversible breakdown of muscle mass which does not respond to nutritional interventions. Patients experience variable symptoms including anorexia, early satiety, and weakness.¹ Common in advanced cancer, it directly causes death in 20% of patients.² Cancer cachexia consists of 3 stages: precachexia, cachexia, and refractory cachexia.¹

Precachexia precedes significant weight loss and manifests as anorexia with impaired glucose tolerance. Cachexia is defined in Table 1.

Refractory cachexia occurs in advanced illness with patients showing poor performance status and a short life expectancy. Current pharmacologic therapies for refractory stages include glucocorticoids, and megesterol acetate. Glucocorticoid effect is short and responses to megesterol are variable. Anamorelin is a ghrelin analogue now studied for the treatment of cancer cachexia. Phase 3 trials patients with advanced lung cancer show that anamorelin improves appetite and muscle mass. This article outlines the pharmacology, pharmacodynamics, and clinical uses of anamorelin.

Ghrelin Physiology

The oxyntic mucosa of the stomach produces ghrelin, a 28-amino-acid peptide hormone.³ Ghrelin targets the growth hormone (GH) secretagogue receptor 1a (GHSR-1).⁴ Receptor

Table 1. Diagnosis of cancer cachexia.

- Weight loss >5% over past 6mo (in absence of simple starvation) or
- Body mass index <20 and any degree of weight loss >2% or
- Appendicular skeletal muscle index consistent with sarcopenia (men: <7.26 kg/m²; women: <5.45 kg/m²)* and any degree of weight loss >2%

Adapted from Fearon et al.¹

*measurements determined by dual energy x-ray absorptiometry.

expression occurs in the central nervous system (CNS) and in peripheral tissues. Peripherally the receptor exists in the pancreas, thyroid, spleen, myocardium, and adrenal glands.⁵ The GHSR-1 lacks expression in liver, skeletal muscle, or adipose tissue.⁶ Ghrelin's actions on skeletal muscle may involve an unidentified receptor which can affect muscle in a GH-axis-independent manner.⁷ Ghrelin dose dependently stimulates food intake in rodents and humans.⁸ The most important clinical aspect of ghrelin is the reversal of anorexia.

CNS effects

In the CNS, GHSR-1 expression is highest in the hypothalamus, specifically the anterior and lateral hypothalamic areas, ventromedial hypothalamus, and arcuate nuclei.⁹ Ghrelin stimulates production of orexigenic mediators such as neuropeptide Y.¹⁰ Ghrelin administration activates ghrelin receptors located



in the arcuate nucleus of the hypothalamus which stimulates food intake.¹¹ Peripherally administered ghrelin likely stimulates the hypothalamus from the periphery through the vagus nerve.^{12–14}

Effect on energy consumption

Ghrelin promotes formation of fat (white adipocytes) and inactivates brown adipocytes.¹⁵ The mechanism of brown adipocyte inhibition is through inactivation of sympathetic nervous system output.¹⁶ Its stimulation of lipogenic pathways through gene expression of lipogenic enzymes, such as acetyl-CoA carboxylase, stearoyl CoA desaturase, and fatty acid synthase, in white adipose tissue leads to adipose formation.¹⁷

Effects on skeletal muscle

Ghrelin acts on muscle through an unidentified receptor.⁷ Ghrelin promotes myocyte differentiation and fusion in myoblast cell cultures.¹⁸ Ghrelin protects muscle from atrophy due to fasting and denervation by activating cellular pathways such as mTOR and Akt signaling.⁷ These protective effects do not involve the GH/insulinlike growth factor 1 (IGF-1) axis.⁷ In Lewis lung carcinoma models, ghrelin enhances the downregulation of ubiquitin-proteasome pathways which contribute to muscle breakdown in cachexia.⁷ Ghrelin protection against muscle atrophy involves reduction in inflammation and increased IGF-1 production.^{19–21}

Effect on cardiac muscle

The main mechanisms through which ghrelin and analogues (GHS) exert their actions on cardiovascular system are as follows: (1) positive inotropic effect, (2) vasodilatation and regulation of endothelium activity, (3) antiapoptotic effects, (4) cardioprotective effects against ischemia and reperfusion injury, (5) reduction in sympathetic activity, and (6) chronic IGF-1-mediated effects.²² Preclinical models of ghrelin analogues suggest that these agents can positively affect increases in lean mass in animal models of congestive heart failure.²³

Anti-inflammatory effects

Ghrelin inhibits expression of inflammation causing cytokines, such as IL-1 α , IL-6, and tumor necrosis factor, thereby reducing inflammation.^{24,25} By inhibiting nuclear factor κ B, anamorelin also reduces production of pro-inflammatory cytokines and stops muscle breakdown (inhibits proteolysis).²⁶ These changes appear to target muscle cells directly.

Endocrine effects

Anamorelin increases GH, with peak effects about 1 hour post-dose. Increases in GH trigger rises in IGF-1 levels which act by

Table 2. Physiologic effects of ghrelin pertaining to anorexia-cachexia.

Increased appetite and food intake
Stimulates production of orexigenic mediators
Stimulates hypothalamus centrally and peripherally
Promotes formation of fat (white adipocytes) and inactivates brown adipocytes
Inhibition of sympathetic nerve system output
Stimulation of lipogenic pathways
Promotes myocyte differentiation and fusion in myoblast cell cultures
Protects muscle from atrophy due to fasting and denervation by activating cellular pathways such as mTOR and Akt signaling
Downregulation of ubiquitin-proteasome pathways
Downregulating inflammation
Increased hepatic production of IGF-1
Stimulates gastrointestinal motility

Abbreviation: IGF-1, insulinlike growth factor 1.

negative feedback through somatostatin to suppress GH secretion in the hypothalamus and pituitary.^{27,28} Both GH and IGF-1 work directly on muscle to counteract effects of cachectic cytokines.²⁹ Levels of prolactin, luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, thyroid-stimulating hormone, and cortisol do not change with administration of anamorelin confirming the selective action on GH increase.^{27,30} Ghrelin is elevated in fasting and reduced in obesity.³¹ Ghrelin inhibits insulin secretion.³² Ghrelin promotes secretion of glucagon from pancreatic α cells.³³ Table 2 summarizes the physiologic effects of ghrelin.

Gastrointestinal

Ghrelin stimulates gastrointestinal motility potentially decreasing nausea and vomiting.³⁴

Tumor growth

In mouse tumor models, such as Lewis lung and human bronchioalveolar carcinoma, anamorelin or ghrelin did not promote tumor growth.³⁰ Table 3 summarizes tumor models where anamorelin did not increase growth.

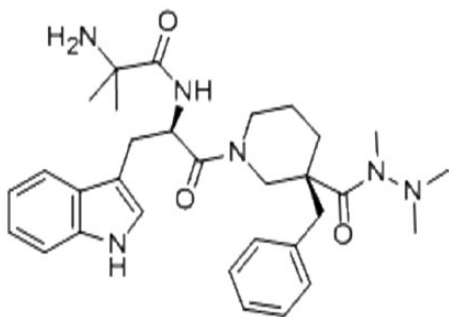
Structure

Anamorelin is a hydrochloride salt with a molecular weight of 583 Da.^{27,30} Its chemical name is 2-amino-*N*-[(2R)-1-[(3R)-3-benzyl-3-[dimethylamino(methyl)carbamoyl] piperidin-1-yl]-3-(1H-indol-3-yl)-1-oxopropan-2-yl]-2-methylpropanamide; hydrochloride.³⁸

Table 3. Effect of GH on tumor growth.

AUTHOR	STUDY SYSTEM	GH/GH ANALOGUE	EFFECT ON TUMOR GROWTH
Khan et al ³⁵	Nude mice, NCI-H358 human bronchioalveolar carcinoma, and MDA-MB-468 human breast adenocarcinoma, subcutaneously implanted in nude mice	Plasmid-mediated GHRH supplementation	No growth, but rather it reduced tumor volume by 40%
Khan et al ³⁶	Lewis lung adenocarcinoma tumor-bearing immunocompetent mice	Plasmid GHRH supplementation	Histopathologic analysis revealed that treated animals were less likely to develop lung metastases than controls (11%) and had no alternate-organ metastases. The number of metastases/lung was reduced by 57% in female mice with GHRH treatment ($P < .006$)
Koo et al ³⁷	5- to 6-wk-old and 16- to 24-mo-old mice inoculated with a transplantable lymphoma cell line, EL4	Nonpeptidyl small m.w. compound, a GHS	Treated old mice showed statistically significant resistance to the initiation of tumors and the subsequent metastases. Immune enhancing

Abbreviations: GH, growth hormone; GHRH, growth hormone–releasing hormone; GHS, GH secretagogue.



Pharmacology

Pharmacodynamics

Anamorelin interacts with the ghrelin receptor with high affinity (0.70 nM) and has no antagonist properties. The affinity of anamorelin is slightly less than natural ghrelin. Anamorelin shows minimal binding to other receptors such as calcium channels, sodium channels, and the serotonin transporter showing its specificity for the ghrelin receptor even at elevated concentrations.³⁹

Pharmacokinetics and Metabolism

Anamorelin is an oral formulation with a half-life of nearly 7 to 12 hours, longer than natural ghrelin.²⁷ In healthy volunteers, peak levels occur at 0.5 to 2.0 hours postdose.²⁷ Plasma clearance of radiolabelled anamorelin shows that most of the drug is excreted in the feces (92%). Food decreases the area under the curve (AUC) of anamorelin by 4-fold.⁴⁰ Metabolism occurs by CYP3A4. CYP3A4 inhibitors such as ketoconazole increase the AUC of anamorelin by 4-fold.⁴⁰

Drug Interactions

Apart from the potential effects of CYP3A4 inhibitors on anamorelin, there have been no reported clinically significant drug interactions.

Adverse Effects

Two randomized controlled trials demonstrate no dose-dependent adverse effects.³⁸ There were no effects on the QTc interval (corrected QT interval).⁴¹ Discolored feces occurred but were unrelated to anamorelin.⁴¹ There were no adverse cardiovascular events.⁴¹ Dosages of 50 mg or greater can cause elevations in hepatic enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which are reversible with drug discontinuation.⁴¹ Headache and gastrointestinal upset occurred in low frequency at doses of 50 mg/d. Diarrhea occurred in 1 patient receiving 75 mg/d. Hyperglycemia occurred in <1% of patients in the phase 3 studies (see below).³⁸ Fatigue and asthenia were the most frequent adverse effects in the anamorelin group, but the contribution of this drug to these symptoms is unclear. Other adverse effects such as atrial fibrillation and dyspnea (5%) occurred in the anamorelin arm, but these were unlikely to be due to the drug.⁴¹ There were no deaths attributable to the drug. Fluid retention is not a reported adverse effect of anamorelin.³⁸

Clinical Studies in Anorexia-Cachexia

Preclinical studies

Rats receiving anamorelin 3, 10, or 30 mg/kg orally once a day for 6 days versus control showed increases in food intake with increasing doses compared with controls.³⁹ There were increases in plasma GH levels as doses of anamorelin increased.³⁹ The maximum plasma GH concentrations occurred at 0.5 to 2 hours postdose. Anamorelin-induced increases in GH and IGF-1 levels occurred in other species such as pigs and dogs.³⁹

Phase 1 studies

Phase 1, randomized, double-blind, placebo-controlled single dose–escalating studies in healthy volunteers showed that doses

of 25 and 50 mg anamorelin causes increased appetite compared with placebo at 30 minutes. Duration of effect was 4 hours. Food intake increased 18.4%, which was significantly greater than placebo. Adverse effects were minimal. The study reported no increased adverse effects with increasing dose and there were no drug discontinuations due to the study drug.⁴¹ Another randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation phase 1 study in 29 healthy volunteers showed absence of dose-limiting adverse effects. Anamorelin 50 or 75 mg caused significant dose-related weight gain after 6 days compared with placebo and versus placebo, with daily dosing leading to the greatest weight gains. The mean gain in weight from baseline after 50 mg daily doses was 1.25 ± 0.73 kg ($P = .0022$ versus placebo), and after 75 mg daily doses, it was 1.16 ± 0.65 kg ($P = .0022$ versus placebo).⁴¹ Circulating GH increased after single 25, 50, and 75 mg doses of anamorelin but then decreased with continued dosing. Doses of 50 and 75 mg caused increases in IGF-1.²⁷ One subject had increases in AST and ALT levels which normalized after discontinuation of the drug. Other adverse effects considered possibly related to study drug anamorelin were nausea, "feeling hot," "stomach discomfort," diarrhea ($n = 1$ for each symptom), and headache ($n = 2$).

Phase 2 studies

A phase 2, multicenter, double-blind, placebo-controlled, crossover study ($N = 16$) evaluated anamorelin 50 mg/d or placebo for 3 days. A 3- to 7-day washout period was followed and treatments were switched. Anamorelin significantly increased body weight (0.77 kg versus -0.33 kg, $P = .016$). Growth hormone, IGF-1, and insulin growth factor -binding protein 3 levels increased significantly in the anamorelin arm, although levels remained within the normal range. Patient-reported symptoms significantly improved. Adverse effects in 4 patients likely related to anamorelin were as follows: hyperglycemia ($n = 2$), nausea ($n = 1$), and dizziness ($n = 1$). Most adverse effects were low grade.⁴⁰ Pooled data from 2 other phase 2, multicenter, randomized, double-blind, placebo-controlled trials which included 82 patients suggest benefit from anamorelin.⁴² The studies used a 3-day crossover design, with patients having *different solid tumors* such as lung, colon, and breast cancers as well as some hematologic malignancies. Pooled data showed weight gain as measured by dual-energy X-ray absorptiometry over 12 weeks. Weight increased 1.89 ± 0.53 kg in the anamorelin group versus a loss of weight (-0.20 ± 0.52 kg) ($P = .0006$) in the placebo group. The study drug caused increases in total body mass, appendicular lean body mass, handgrip strength and quality of life (QoL) occurred. Scale weight increased and inflammatory cytokines decreased in the anamorelin group although not significantly. Both IGF-1 and insulin growth factor-binding protein 3 showed increases at weeks 4, 8, and 12 but remained within normal ranges. In this study, patients

tolerated anamorelin well, and adverse effects were similar between treatment arms.⁴² Finally, a randomized, placebo-controlled, multicenter, phase 2 trial evaluated anamorelin 50 mg ($n = 76$), 100 mg ($n = 73$) versus placebo ($n = 77$) on weight, handgrip strength, QoL, and MD Anderson Symptom Inventory (MDASI) score over 12 weeks. Patients receiving anamorelin 100 mg group gained 0.14 kg. Both the 50 mg group and placebo group experienced weight loss (mean losses of 0.3 and 1.32 kg for the 50 mg and placebo groups). The average difference in weight between the anamorelin 100 mg arm and placebo was 1.47 kg ($P = .0005$). There were improvements in handgrip strength and MDASI scores in the anamorelin 100 mg dose group, although these did not reach statistical significance. Anamorelin was safe and well tolerated in this study, and adverse events (AEs) of anorexia, nausea, and fatigue were reported in fewer anamorelin-treated than placebo-treated patients.³⁸

Phase 3 studies

The 2 clinical studies (ROMANA) evaluated anamorelin for anorexia-cachexia in non-small-cell lung cancer (NSCLC) (stage III/IV). The studies measured the effect of anamorelin on lean body mass, QoL, physical strength (handgrip), and biochemical markers. Both studies were multisite double-blind, placebo-controlled parallel group studies. Patients received either 100 mg anamorelin or placebo, orally, daily for 12 weeks.³⁸ Inclusion criteria included ECOG (Eastern Cooperative Oncology Group) performance score of 0 to 2 and cachexia ($\geq 5\%$ weight loss within 6 months or body mass index < 20 kg/m²). Randomization was (2:1) to 100 mg anamorelin or placebo. Oncology therapies were allowed during the study. Co-primary end points were changes in lean body mass (measured by dual-energy X-ray absorptiometry) and handgrip strength over 12 weeks. Secondary end points included changes in body weight and anorexia as measured by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Safety was assessed. In ROMANA 1 ($n = 484$), patients taking anamorelin experienced a median increase in body mass of 1.10 kg in 12 weeks, compared *with a loss* of 0.44 kg for the placebo group. Body weight rose by an average of 2.2 kg in the anamorelin arm, compared with 0.14 kg in the placebo arm of the study. Appetite also significantly improved over 12 weeks in patients taking anamorelin. The most frequent drug-related AEs included hyperglycemia and nausea, which were the most frequent adverse effects in the study. Handgrip strength increased only in male participants receiving anamorelin. In ROMANA 2, 495 with advanced NSCLC experienced similar benefits including an average weight gain of 0.95 kg in the anamorelin arm and an average loss of 0.57 kg for those receiving placebo. Again, symptoms of anorexia improved in the anamorelin arm over 12 weeks. *There were no improvements in handgrip strength in*

Table 4. Anamorelin studies.

AUTHOR	STUDY DESIGN	CANCER TYPE, STAGE	N	INTERVENTION, ANAMORELIN DOSE	OUTCOMES	COMMENT
Garcia et al (2013) ⁴⁰	Randomized crossover trial	7/16 lung, rest colon, breast, prostate, rectal, transitional cell, non-Hodgkin lymphoma	Anamorelin → placebo (n=9) Placebo → anamorelin (n=7)	50 mg, placebo	Anamorelin significantly increased body weight compared with placebo (food intake increased but not significantly)	Patient-reported symptoms, including appetite as measured by ASAS, significantly improved with anamorelin (8.1 versus 1.0 for placebo)
Garcia et al (2015) ⁴²	RCT Aggregate of 2 completed phase 2, multicenter, placebo-controlled, double-blind trials	Breast, colon, lung prostate renal. Patients in both arms did receive bevacizumab	74	50 mg, placebo	Over 12 wk, lean body mass increased in 38 patients in the anamorelin group by a least-squares mean of 1.89 kg compared with a decrease in a least-squares mean of -0.20 kg for 36 patients in the placebo (P=.0006)	The most common grade 3 to 4 adverse events (treatment-related or not) in the anamorelin group were fatigue, asthenia, atrial fibrillation, and dyspnea
Temel et al (2016) ³⁸	RCT	Stage III or IV NSCLC	484 ROMANA 1 (323 to anamorelin, 161 to placebo), 495 patients were enrolled in ROMANA 2 (330 to anamorelin, 165 to placebo)	Anamorelin 100 mg, placebo	Over 12 wk, lean body mass increased in patients assigned to anamorelin compared with those assigned to placebo in ROMANA 1 (median increase 0.99 kg versus -0.47 kg P<.0001) and ROMANA 2 (0.65 kg versus -0.98 kg, P<.0001)	No increase in handgrip strength. Hyperglycemia was the most common adverse effect
Takayama et al (2016) ⁴⁴	RCT	Inoperable stage III or IV NSCLC or relapsed NSCLC	56 in 50 mg arm, 55 in 100 mg arm 60 in placebo	Anamorelin 50, 100 mg, placebo	The changes in body weight were -0.93, 0.54, and 1.77 kg in the placebo, 50-mg anamorelin, and 100-mg anamorelin groups, respectively	No improvement in handgrip strength. 100 mg should be the dose for future studies

Abbreviations: NSCLC, non-small-cell lung cancer; RCT, randomized controlled trial; ASAS, anderson symptom assessment scale.

ROMANA 2. Adverse effects were similar to those in *ROMANA 1.* A recent meta-analysis⁴³ confirmed the above studies and suggested that the heterogeneity of the study populations may have affected outcomes and also suggested results may have been dose related. Table 4 summarizes key clinical studies with anamorelin.

Safety

ROMANA 3 evaluated safety and adverse effects for patients completing *ROMANA 1* and *ROMANA 2.* Of the 703 patients who completed *ROMANA 1* and *ROMANA 2,* 513 patients entered *ROMANA 3* (anamorelin, N = 345; placebo, N = 168). During *ROMANA 3,* anamorelin and placebo groups had similar incidences of treatment-related AEs (52.2% versus 55.7%), grade ≥3 adverse effects (22.4% versus 21.6%), and serious adverse effects (12.8% versus 12.6%). There were 36 (10.5%) and 23 (13.8%) deaths in the anamorelin and

placebo groups, respectively; none were drug related. Improvements in body weight and symptoms of anorexia observed in the original trials were maintained over 12 to 24 weeks. Anamorelin, versus placebo, significantly increased body weight from baseline of original trials at all time points (P<.0001) and improved symptoms of anorexia at weeks 3, 6, 9, 12, and 16 (P<.05). No significant improvement in handgrip strength occurred in either group.⁴⁵

Schedule of Administration

Anamorelin was dosed at 100 mg/d orally in the *ROMANA* studies.

Conclusions

Anamorelin is a selective ghrelin receptor agonist mimicking the hormone. In phase 3 studies, anamorelin reverses symptoms of anorexia and increases lean body mass in patients with

advanced lung cancer. It represents a new option for the management of cancer anorexia-cachexia.

Author Contributions

EP was the only contributor to this article.

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