The Potential of Ghrelin in Cancer Anorexia–Cachexia

Jose M Garcia,[1] Aminah Jatoi[2] and Egidio Del Fabbro[3]

1. Assistant Professor, Michael E DeBakey Veterans Affairs Medical Center, Division of Endocrinology, Diabetes, and Metabolism, Departments of Medicine and Molecular and Cell Biology, Huffington Center on Aging, Baylor College of Medicine, Houston, Texas, US; 2. Professor, Department of Oncology, Mayo Clinic, Rochester, Minnesota, US; 3. Associate Professor, Director, Palliative Care Program, Division of Hematology, Oncology and Palliative Care, Department of Internal Medicine, Massey Cancer Center, Virginia Commonwealth University, Virginia, US

Abstract

The cancer anorexia–cachexia syndrome (CACS) is often seen in patients with incurable malignancies and is associated with increased mortality, decreased efficacy of anticancer treatments and poor quality of life. However, there are currently no effective therapies for CACS. Since CACS is a multifactorial syndrome with a complex pathophysiology, therapeutic interventions for CACS might potentially include anabolic agents as well as anti-inflammatory effects. Ghrelin affects numerous key pathways in the regulation of body weight and body composition through increased appetite and growth hormone (GH) secretion. Preliminary clinical data indicate that the administration of ghrelin and ghrelin receptor agonist such as anamorelin have beneficial effects on appetite and body weight in patients with CACS. Anamorelin is currently in phase III clinical trials.

Keywords

Anamorelin, cancer anorexia–cachexia syndrome, ghrelin

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Correspondence: Jose M Garcia, Assistant Professor, Michael E DeBakey Veterans Affairs Medical Center, Division of Endocrinology, Diabetes and Metabolism, Departments of Medicine and Molecular and Cell Biology, Huffington Center on Aging, Baylor College of Medicine, 2002 Holcombe Blvd, Houston, Texas, 77030, US. E: jgarcia1@bcm.edu

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Cachexia is a complex metabolic disorder that results in progressive weight loss, muscle and adipose tissue wasting and inflammation and is frequently observed in patients with incurable malignancies.[1] Weight loss in cancer patients results from reduction in adipose tissue and skeletal mass. Anorexia is defined as the loss of desire to eat. Although anorexia frequently accompanies cachexia, there does not appear to be a cause–effect relationship between the two. Anorexia occurs in almost half of patients with cancer,[2,3] and can be present even in patients not receiving chemotherapy.[4] Although our understanding of cachexia has increased over the last decade, lack of consensus on its definition, diagnostic criteria and classification have impaired the development of therapeutic interventions. In 2011, an international consensus panel defined cancer anorexia–cachexia syndrome (CACS) as a multifactorial group of signs and symptoms defined by ongoing loss of skeletal muscle mass (with or without loss of fat mass) and by the fact that these changes are not able to be fully reversed by conventional nutritional support. The result of this detrimental process is functional impairment and early demise.[5]

The incidence of CACS depends on the tumour type and ranges from 16 % to over 50 % of patients.[6,7] The degree of severity also varies, with loss of more than 10 % body weight in 15 % of patients.[8] The highest incidence occurs in patients with solid tumours, in particular pancreatic and gastric cancers, where weight loss is seen in over 80 % of patients. The lowest incidence is seen in patients with non-Hodgkin lymphoma, breast cancer, acute non-lymphocytic leukaemia and sarcomas.[9] More than 50 % of patients with cancer die with CACS being present.[7] It should be noted, however, that the percentage above are heavily influenced by the scope of practice or clinical setting from which they have been derived, and, in this review, we point out that CACS is by definition observed in patients with advanced, incurable malignancies.

CACS is associated with poor QoL,[1,10–13] poor physical function,[10,12] decreased response to therapy,[14,15] decreased tolerance to therapy[1,5,16] and poor prognosis.[9,10,17,18] A meta-analysis of 30 randomised controlled trials from the European Organisation for Research and Treatment of Cancer (EORTC) found a significant correlation between poor appetite and poor prognosis.[19] The predictive value of CACS is independent of disease stage and performance status.

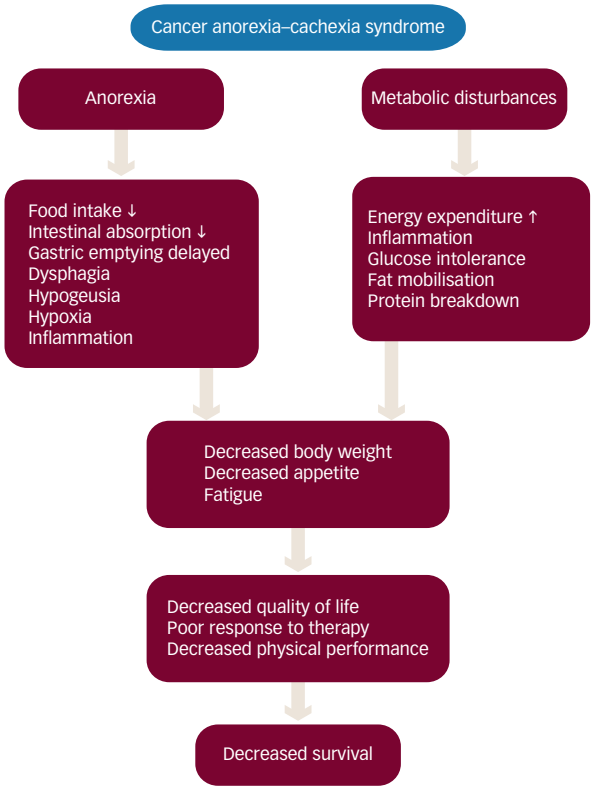
Diagnostic criteria for CACS were recently established by a consensus group and are summarised in *Table 1*. The same group concluded that cachexia progresses through three stages. Precachexia involves a weight loss ≤5 %, anorexia and metabolic change. Cachexia comprises a weight loss >5 % or body mass index (BMI) <20 and weight loss >2 %

Table 1: Diagnostic Criteria for Cancer Anorexia–Cachexia Syndrome Source[6]

Criteria
Weight loss ≥5 %
Or body mass index <20 and weight loss >2 %
Or sarcopenia and weight loss >2 %
Reduced food intake
Systemic inflammation

Sarcopenia is defined as absolute muscularity below the fifth percentile. This can be assessed as follows: mid-upper-arm muscle area by anthropometry (men <32 cm^2; women <18 cm^2); appendicular skeletal muscle index determined by dual-energy X-ray absorptiometry (men <7.26 kg/m^2; women <5.45 kg/m^2); lumbar skeletal muscle index determined by computed tomography imaging (men <55 cm^2/m^2; women <39 cm^2/m^2); whole body fat-free mass index without bone determined by bioelectrical impedance (men <14.6 kg/m^2; women <11.4 kg/m^2).

Figure 1: Pathophysiology of Cancer Anorexia–Cachexia Syndrome[22,59]



or sarcopenia and weight loss >2 %. In refractory CACS, reversal of weight loss is no longer possible since the cancer is both procatabolic and is unresponsive to treatment. Refractory CACS is characterised by a low performance score (World Health Organization [WHO] 3 or 4) and an expected survival of less than 3 months.[5] However, it must be stressed that CACS is a continuum and not all patients traverse the entire spectrum. Importantly, these criteria have not been validated clinically, but they provide a meaningful scaffold that may lead to future research. Recently published retrospective data found that, before the publication of these criteria, CACS was under-diagnosed. While 49 % of the sample cohort met at least one of the weight criteria for CACS, only 5 % were prescribed medication for the condition.[20] There are currently no standard effective treatments for CACS,[10] although it affects most metastatic cancer patients at some point during their disease course. This article aims to review the clinical features and pathogenesis of CACS, the role of ghrelin and its potential as a therapeutic strategy in CACS.

Pathophysiology and Clinical Features of Cancer Anorexia–Cachexia Syndrome

Clinical features of CACS include weight loss in adults or growth failure in children (excluding endocrine disorders), anorexia, inflammation, insulin resistance and increased muscle protein breakdown.[21] There is often reduced food intake and systemic inflammation. It is a multi-organ syndrome that involves the liver, heart and fat, but its most important target is skeletal muscle, since this represents over 40 % of total body weight.[22] The weight loss associated with CACS is a result of altered metabolism with decreased energy intake (reduced appetite, early satiety, changes in taste/smell) and possibly also changes in energy needs.[5,23] Other symptoms associated with CACS include anaemia, hypogonadism, immunodepression, resistance to antineoplastic agents and increased treatment-related toxicities.[5,24]

The pathophysiological changes responsible for these symptoms are summarised in *Figure 1* and can be attributed to tumour-derived factors, cytokines and neuroendocrine changes. Other factors that contribute to anorexia include altered taste perception, side effects of therapy and psychological factors, including depression.[23] CACS is associated with an increase in muscle protein degradation,[26] largely mediated by the ubiquitin–proteasome pathway[26] and a decrease in protein synthesis.[27] There is an increase in lipolysis, leading to a loss of adipose tissue.[28,29] Furthermore, interaction between host cells and cancer cells causes the release of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), IL-6 and IL-8. These stimulate proteolytic pathways, resulting in muscle atrophy and the breakdown of adipose tissue.[30] They also increase basal energy expenditure[31] and induce anorexia.[32]

The pathogenesis of cancer anorexia is caused by the inability of the hypothalamus to respond appropriately to peripheral signals, resulting in an imbalance between orexigenic (i.e. appetite stimulating) signals, such as neuropeptide Y (NPY) and anorexigenic signals, such as proopiomelanocortin (POMC). NPY stimulates parasympathetic activity and decreases resting energy expenditure, while POMC increases sympathetic activity and increases resting energy expenditure.[8] Cytokines, including IL-1 and TNF-α, appear to mediate this effect.[33,34]

The Importance of Treating Cancer Anorexia–Cachexia Syndrome

Since CACS is associated with a poor prognosis, it is important to try to treat the condition, with the aim of improving symptoms and possibly also improving survival. Treatment goals in CACS include improvements in appetite, lean body mass, resting energy expenditure, quality of life (QoL), performance status and reduction of the levels of pro-inflammatory cytokines.[1,12] The European Palliative Care Research Collaboration (EPCRC) has developed evidence-based recommendations for the classification and treatment of CACS in advanced cancer patients. As a minimal goal, body weight should be maintained and further loss prevented.[36] Early diagnosis is central to managing disease progression and preventing unnecessary deterioration in QoL.[5]

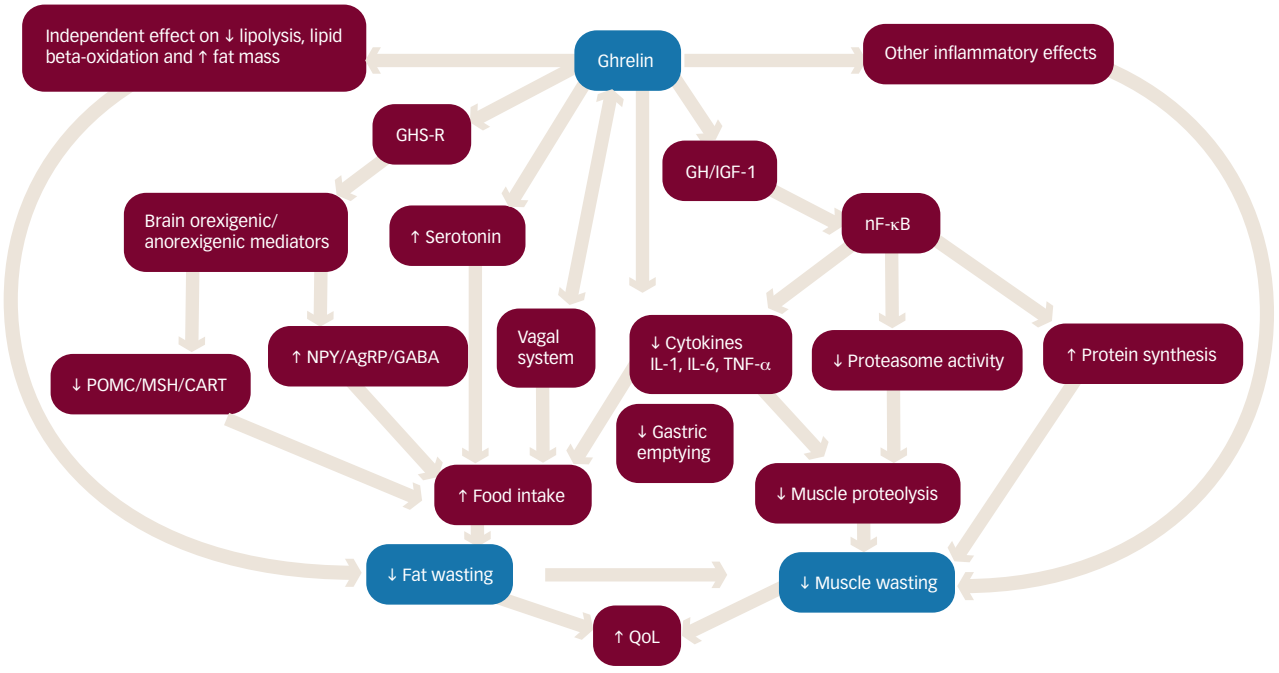
Treatment options for CACS are limited and there are no standard effective treatments for this indication. Patients do not appear to benefit from nutritional supplementation alone; patients on complete parenteral nutrition still undergo weight loss, emphasising the metabolic role in CACS.[8,36,37] Corticosteroids and progestational agents, such as megestrol acetate, are the most widely used treatment options but only partially alleviate CACS.[38–41] Corticosteroids may be beneficial

Table 2: Currently Available and Emerging Pharmacological Treatment Approaches to Cancer Anorexia–Cachexia Syndrome

Drug	Level of Evidence	Reference
Megestrol acetate/medroxyprogesterone acetate	Approved in few European countries but limited efficacy	38, 39, 41
Corticosteroids	Limited efficacy	40
Omega-3 fatty acids	Mixed results in clinical trials	94
Cannabinoids (dronabinol)	Limited evidence	45, 95
Thalidomide	Effective only in patients with advanced pancreatic cancer	96
Ghrelin agonists:		
Anamorelin	Phase III clinical trials underway	89
Macimorelin	Clinical trial programme started	90
Capromorelin	Has been investigated in studies of ageing	91, 92
DIn-101	Phase I clinical trial started	93
COX-2 inhibitors (celecoxib)	Promising data in pilot study	97
Olanzapine	Preclinical studies	98
Anabolic steroids (oxandrolone)	Showed efficacy in a phase III clinical trial	99
BCAA	Preclinical studies	100
Melancortin-4 receptor agonists	Preclinical studies	101
β2 agonists (formoterol fumarate)	Preclinical studies	102
Anti-myostatin peptibody	Preclinical studies	103
Anti-IL-6 antibodies (Tocilizumab)	Isolated case report but further study warranted	104
SARMs (enobosarm)	Phase II studies	105–108
	Phase III trial failed to meet endpoints	109
IL-1 receptor antagonist (IP-1510)	Phase I/II study (n=17) showed promising data	110
Insulin	Evidence of palliative role	43

BCAA = branched chain amino acids; COX-2 = cyclooxygenase-2; IL = interleukin; SARMs = selective androgen receptor modulators.

Figure 2: Mechanism of Action of Ghrelin in Cancer Anorexia–Cachexia Syndrome[22]



AgRP = agouti-related protein; CART = cocaine- and amphetamine-regulated transcript; GABA = γ-aminobutyric acid; GH = growth hormone; GHS-R = growth hormone secretagogue receptor; IGF = insulin-like growth factor; IL = interleukin; MSH = melanocyte-stimulating hormones; nF-kB = nuclear factor-κB; NPY = neuropeptide Y; POMC = proopiomelanocortin; QoL = quality of life; TNF = tumour necrosis factor.

for stimulation of appetite in patients with refractory CACS. Recent evidence has also suggested a role for insulin resistance in CACS;[42] insulin treatment has been found to potentially play a palliative role in CACS.[43]

To effectively treat CACS, it is important to target both tumour and host factors. Current and emerging therapeutic options for CACS are summarised in *Table 2*. Drugs with a strong rationale that have not demonstrated consistent and convincing efficacy in clinical trials to date include eicosapentaenoic acid,[44] cannabinoids,[45] bortezomib[46] and anti-cytokine therapies including thalidomide[47] and anti-TNF-alpha MoAb (infliximab).[46] A recent clinical trial failed to show any benefit for melatonin.[48] However, following advances in understanding of the pathological processes underlying CACS, several targeted

Table 3: Summary of Clinical Studies Testing the Efficacy and Safety of Anamorelin as a Therapeutic Option for Cancer Anorexia–Cachexia Syndrome

Trial Description	No.	Cancer Type	Results	Reference
Pilot study Multicentre, randomised, double-blind, placebo-controlled, crossover study, 3 days, 3–7 day washout, then therapies switched	16	Various	Anamorelin significantly increased body weight compared with placebo (0.77 kg versus –0.33 kg). Food intake increased but not significantly. GH and IGF-1 significantly increased with anamorelin. Patient-reported appetite significantly improved with anamorelin (8.1 versus 1.0 for placebo). AEs in 4 patients possibly related to anamorelin: hyperglycaemia (n=2), nausea (n=1) and dizziness (n=1). Most AEs were mild	86
Phase II study Multicentre, randomised, double-blind, placebo-controlled, 12 weeks	81	Various	Total and lean body mass significantly increased versus placebo at weeks 4 and 8; the increase was stable from weeks 4 to 12. Significant increase in handgrip strength at week 8. SAEs 32 % anamorelin versus 26 % placebo	87
Phase I study Single-centre, randomised, double-blind, placebo-controlled Panel A subjects (n=8) received placebo or anamorelin 25 mg qd, for 5 days. Panel B subjects received anamorelin, 25 mg bid or 50 mg qd, for 6 days then crossed over to the other dosage for 5 days (n=12); 3 subjects received placebo for all 11 doses to maintain double-blinding. Panel C subjects (n=9) received placebo or anamorelin, 75 mg qd, for 6 days	29	Healthy volunteers	Subjects who received anamorelin, 50 or 75 mg, had significant dose-related weight gain after 6 days versus placebo, with the greatest increases seen with daily dosing The mean increase in weight from baseline after 50 mg qd was 1.25 ± 0.725 kg (p=0.0022 versus placebo), and after 75 mg qd it was 1.16 ± 0.651 kg (p=0.0022) One subject in the 50 mg qd group had moderate transient elevation in aspartate aminotransferase and alanine aminotransferase levels. No other AEs were reported	85
Phase II study. Multicentre, randomised, double-blind, placebo-controlled, 12 weeks; anamorelin 100 mg or 50 mg once daily, or matching placebo (1:1:1)	226	NSCLC	The anamorelin group gained an average of 0.14 kg in weight from baseline, compared with mean losses of 0.3 kg and 1.32 kg for the 50 mg and placebo, groups, respectively; mean treatment difference between 100 mg anamorelin and placebo was 1.47 kg (p=0.0005)	88
ROMANA 1 Phase III study, 100 mg anamorelin versus placebo, 12 weeks	477*	NSCLC	Results expected February 2014	89
ROMANA 2 Phase III 100 mg anamorelin versus placebo, 12 weeks	477*	NSCLC	Results expected late 2013	89
ROMANA 3 Safety extension study	300*	NSCLC	Results expected 2014	89

**Estimated enrolment numbers. Bid = twice daily; GH = growth hormone; IGF = insulin-like growth factor; NSCLC = non-small cell lung cancer; qd = once daily; ROMANA = Safety and Efficacy of Anamorelin HCl in Patients With Non-Small Cell Lung Cancer-Cachexia; SAEs = serious adverse events.*

therapies are in clinical development. These include anti-IL-6 antibodies, cytokine antagonists, myostatin inhibitors, selective androgen receptor modulators and ghrelin receptor agonists.[46,49] Of these, the largest body of clinical data to date describes the efficacy and safety of ghrelin.

The Role of Ghrelin in Cancer Anorexia–Cachexia Syndrome

Ghrelin is a gastric hormone secreted in response to fasting. It stimulates appetite and increases food intake and is the endogenous ligand for the ghrelin receptor (GRLN receptor, also known as growth hormone [GH] secretagogue receptor-1a).[50,51] Circulating ghrelin exists in two forms: acylated ghrelin (the biologically active form that binds and activates the GRLN receptor and des-acyl ghrelin (a form that lacks biological activity at the GRLN receptor although it has recently been suggested that it has biological activity by binding a yet unidentified receptor).[52,53] Ghrelin plays a major role in a number of physiological processes including stimulation of GH secretion and regulation of energy homeostasis by a GH-independent mechanism.[54,55] Increased GH secretions stimulates the production of insulin-like growth factor-1 (IGF-1). Together, GH and IGF-1 promote anabolism and increase muscle strength.

Ghrelin has multiple roles in the regulation of energy balance (see *Figure 2*). Although its mechanism of action is not fully understood, its action appears to involve a central hypothalamic mechanism, as well as metabolic and anti-inflammatory effects. It stimulates food intake by blocking anorexigenic mediators and stimulating the production of orexigenic substances.[56,57] It also activates the mesolimbic dopamine system in the hypothalamus, affecting feeding behaviour.[58] Another important role of ghrelin involves its anti-inflammatory actions.[34,59] Ghrelin suppresses the production of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and stimulates the production of anti-inflammatory cytokines (IL-10).[60,61] Ghrelin also inhibits the activation of nuclear factor-κB (NF-KB), a transcription factor that stimulates the production of numerous proinflammatory cytokines and may be involved in protein degradation.[62] In terms of metabolic effects, ghrelin promotes adiposity through the activation of lipogenic pathways in the central nervous system.[34,63] Ghrelin activates white adipocytes, while inactivating brown adipocytes, resulting in decreased energy expenditure.[64] It also promotes lipogenesis and decreases lipolysis and lipid oxidation in white adipose tissue in an animal model of cisplatin-induced cachexia.[65] Other physiological actions of ghrelin include stimulating gastric emptying,[66] increasing cardiac output and decreasing blood pressure.[67] Ghrelin also stimulates the release of endogenous nitric oxide, which may partly mediate its anti-inflammatory and orexigenic actions.[68,69] The combination of these actions suggests that ghrelin may have therapeutic benefits in CACS.

Data between the association between ghrelin levels and CACS are contradictory, partly due to heterogeneity of the study populations. Although one study reported reduced plasma ghrelin concentrations

in cancer patients,[70] total ghrelin levels in CACS patients with gastric, colon, breast and lung cancer were significantly higher than levels in patients without CACS.[71–73] Furthermore, CACS has been associated with an increase in acylated ghrelin and ratio of acylated to total ghrelin levels.[74] The same study suggested that CACS could be a state of ghrelin resistance. It is also possible that ghrelin levels increase to compensate for the increased metabolic rate and energy that is often observed in patients with CACS.[75] Hence, it has been suggested that administration of exogenous ghrelin or ghrelin receptor agonists may have therapeutic value for muscle wasting in CACS.[22,34]

Clinical Use of Ghrelin in the Treatment of Cancer Anorexia–Cachexia Syndrome

Preliminary studies in healthy humans have shown that ghrelin stimulates the release of GH,[76] enhances appetite and results in increased food intake.[77] No serious adverse events (SAEs) were reported in these studies. In a small randomised, placebo-controlled crossover trial, ghrelin demonstrated a stimulatory effect on food intake in CACS, with an increase in patients' meal appreciation score.[78] No AEs were observed.

In a randomised, placebo-controlled, double-blind, double-crossover study of patients with CACS, nutritional intake or eating-related symptoms did not differ significantly between the ghrelin- and placebo-exposed groups, but an increase in patients' meal appreciation, as measured by a visual analogue scale score, was observed in the ghrelin group.[79] In a study of patients with solid gastrointestinal tumours, patients were randomised to either high-dose (13 μg/kg daily) or low-dose (0.7 μg/kg daily) ghrelin for 8 weeks. Appetite scores were increased significantly in the high-dose group and this group manifested a relative maintenance of whole body fat.[80]

In a phase II study, ghrelin therapy resulted in increased food intake, significantly better global health status scores, reduced nausea and vomiting and decreased appetite loss compared with placebo. In addition, ghrelin was associated with fewer AEs during chemotherapy and reduced duration of hospital stay.[81] In another phase II study in patients with gastric cancer, short-term administration of synthetic ghrelin was safe, lessened postoperative body weight loss and improved appetite and food intake after total gastrectomy.[82]

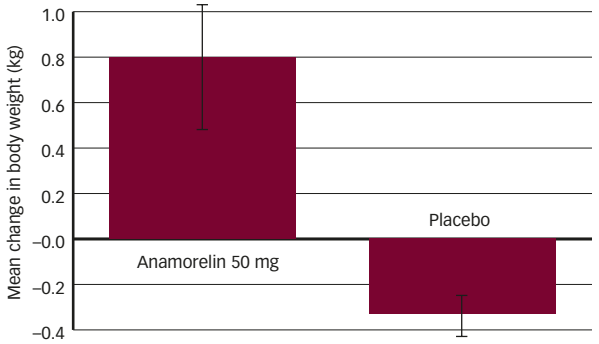
Ghrelin has a very short half-life (<30 minutes) and requires parenteral administration. Studies are therefore investigating the use of ghrelin receptor agonists that have longer half-life and good bioavailability.[34]

The Clinical use of Ghrelin Receptor Agonists

Anamorelin (Helsinn) is a novel, orally active, non-peptidic ghrelin receptor agonist that demonstrated efficacy and safety in preclinical trials,[83] and in healthy volunteers increased body weight and GH secretion with good tolerability.[84,85]

Clinical trial data on the safety and efficacy of anamorelin are summarised in *Table 3*. A multicentre, double blind, placebo-controlled, crossover study evaluated the effects of anamorelin in 16 patients with different cancers and CACS. Anamorelin significantly increased body weight, GH, IGF-1, insulin-like growth factor-binding protein 3 (IGFBP-3) and patient-reported symptoms, including appetite compared with placebo (see *Figure 3*).[86] Mild treatment-related AEs were reported in 25 % of patients. In a phase II study of anamorelin, 81 patients were treated for 12 weeks. At 8 weeks, there was an increase in lean body mass and total body mass, as well as a significant increase in handgrip strength. There was

Figure 3: Mean Change in Body Weight after Anamorelin 50 mg/day or Placebo for 3 Days[86]



p=0.016. Anamorelin n=15; placebo n=16.

no significant difference in QoL and AEs between treatment and placebo arms.[87] A recent phase II study investigated the efficacy and safety of anamorelin in patients with non-small cell lung cancer (NSCLC). Patients (n=226) were randomised to anamorelin 100 mg or 50 mg once daily or placebo for 12 weeks. The 100 mg anamorelin group gained an average of 0.14 kg in body weight from baseline compared with mean losses of 0.3 kg and 1.32 kg for the 50 mg and placebo groups, respectively. The mean treatment difference between 100 mg anamorelin and placebo was 1.47 kg (p=0.0005). A similar percentage of patients reported at least one treatment-emergent AE in the placebo (93.5 %), 50 mg (93.4 %) and 100 mg (94.5 %) treatment arms, and the majority were unrelated to the study medication.[88]

Three trials: Safety and Efficacy of Anamorelin HCl in Patients With Non-Small Cell Lung Cancer–Cachexia (ROMANA 1 and ROMANA 2), and an extension study (ROMANA 3) are currently ongoing. These are phase III trials in patients with unresectable stage III/IV NSCLC and CACS. In these trials, CACS is defined as involuntary weight loss of ≥5 % body weight within 6 months prior to screening or a screening BMI <20 kg/m^2. Patients will receive once-daily oral doses of anamorelin or placebo for 12 weeks. The primary endpoints of ROMANA 1 and 2 are lean body mass and muscle strength, as measured by handgrip strength. Secondary endpoints include body weight, QoL and overall survival. The primary endpoints of ROMANA 3 are concerned with safety and tolerability.[89]

Concern has been expressed that ghrelin may increase growth factors, such as GH and IGF-1, with a resulting stimulation of tumour growth. Furthermore, ghrelin itself may have a mitogenic potential.[59] However, a recent study found that neither anamorelin nor ghrelin promoted tumour growth in an animal model, despite increased levels of GH and a trend of increased IGF-1.[83]

An oral ghrelin receptor agonist, macimorelin, is currently under investigation. An ongoing randomised clinical trial will explore whether macimorelin is effective and well tolerated in patients with CACS.[90] Other agents in development include capromorelin.[91,92] A naturally occurring splice variant of ghrelin, Dln-101, has also received approval to start phase I clinical trials, based on positive data from preclinical trials.[93] Further trials are needed to establish the role of these agents in CACS.

Summary and Concluding Remarks

Since CACS is a multifactorial syndrome with a complex pathophysiology, therapeutic interventions for CACS might include anabolic effects as

well as anti-inflammatory effects or, in essence, targeting more than one therapeutic pathway. A growing body of evidence indicates that ghrelin increases appetite and body weight and preserves lean body mass by decreasing protein degradation. In addition, ghrelin has numerous anti-inflammatory and metabolic effects. There is a need to generate more clinical trial data to support the role of ghrelin receptor agonists in the treatment of CACS. Results to date indicate that anamorelin is effective at stimulating appetite and increasing body weight, as well as being safe and well tolerated – results of large phase III clinical trials are eagerly awaited. ■

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