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Review Article

Treatment of Cachexia: An Overview of Recent Developments

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A B S T R A C T

Body wasting in the context of chronic illness is associated with reduced quality of life and impaired survival. Recent clinical trials have investigated different approaches to improve patients' skeletal muscle mass and strength, exercise capacity, and survival in the context of cachexia and body wasting, many of them in patients with cancer. The aim of this article was to summarize clinical trials published over the past 2 years. Therapeutic approaches discussed include appetite stimulants, such as megestrol acetate, L-carnitine, or melatonin, anti-inflammatory drugs, such as thalidomide, pentoxyphylline, or a monoclonal antibody against interleukin-1α as well as ghrelin and the ghrelin agonist anamorelin; nutritional support, and anabolics, such as enobosarm and testosterone.

Changes in body composition that occur with chronic diseases are usually considered unwanted and are associated with loss of skeletal muscle mass, fat mass, or both.[1,2] The loss of lean and fat tissue may in turn be associated with weight loss. Such involuntary weight loss has been termed *cachexia*. Much confusion exists with regard to the different terminology.[3] A recent consensus definition suggests to diagnose cachexia when there is loss of more than 5% of body weight over 12 months or less in the presence of a chronic illness such as heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, or cancer,[4] altogether providing the basis for an estimated 9 million subjects being affected by cachexia in industrialized countries alone.[5] The mere loss of skeletal muscle mass in the limbs that exceeds 2 SDs of the mean of a healthy young reference population has been termed *sarcopenia*.[6–8] Some researchers have suggested to restrict the use of the term sarcopenia to apparently healthy elderly subjects who lose muscle mass as a consequence of the aging process. In the context of chronic illness, the terms muscle wasting, myopenia, or even muscle wasting disease have been used or proposed.[9,10] In contrast to cachexia, sarcopenia and muscle wasting are not usually associated with weight loss, but with reduced exercise capacity and reduced quality of life.[11] Although the development of cachexia is mostly associated with impaired survival, the development of sarcopenia can be associated with poor survival as well. The 2 conditions have seen much attention in recent years: first, with regard to their definition[4,6]; second, with regard to their pathophysiology[12–14]; and third, with regard to their treatment.[15,16] In fact, pathophysiological pathways of the 2 clinical entities can, but do not necessarily have to, overlap. For clinicians actively involved in the care of patients at risk of cachexia or muscle wasting (ie, surgeons, oncologists, nephrologists, cardiologists, and many more), the available terms often create more confusion than help, making the diagnosis of cachexia and muscle wasting a rarity.[17] This is unfortunate, in particular because both require medical attention, and treatment approaches are currently under way that will hopefully enable physicians to maintain their patients' muscle mass and body weight and therefore their ability to maintain activities of daily living for longer than is currently possible. The aim of this article was to highlight clinical intervention trials that have been published over the past 2 years with the primary purpose of treating cachexia. Studies that have shown beneficial results in animal experiments only using approaches such as myostatin blockade,[18] use of green tea,[19] ursodeoxycholic acid,[20] or inhibition of nuclear factor-κB[21] are not discussed.

Appetite Stimulants

Loss of appetite appears in many patients with cancer, which is not only frequent, but also associated with poor prognosis and reduced quality of life. The origin of appetite loss has been deemed multifactorial, and a recent study failed to show a genetic association of appetite loss in patients with cancer.[22] However, overexpression of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, tumor

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necrosis factor, or interferon-γ, as well as macrophage inhibitory cytokine-1/growth differentiation factor 15 (MIC-1/GDF-15) appear to be involved.[23,24] Activation of these factors has effects on peripheral (lipolysis, proteolysis, insulin resistance) as well as on central pathways (hypothalamic appetite regulation).[23,25] Megestrol acetate, a synthetic, orally active derivative of the hormone progesterone, was originally synthesized in 1963 as a contraceptive drug.[26] Beginning in 1967, it was used in the treatment of breast cancer. Beginning in 1993, it was approved in the United States and in several European countries for the treatment of the anorexia-cachexia syndrome.[26] It has recently been argued that the use of megestrol acetate also may be helpful in patients with muscle wasting without weight loss.[15]

Wen et al[27] recently studied 102 patients with cancer-related anorexia/cachexia syndrome who were randomly assigned to receive, for 8 weeks, either a combination therapy of oral megestrol acetate at a dosage of 160 mg twice daily plus oral thalidomide 50 mg twice daily or megestrol acetate 160 mg twice daily alone (all studies discussed in the text are summarized in Table 1). Patients in either group showed an increase in their appetite score (both $P < .03$). The increase in body weight and the improvement in quality of life were more pronounced in the group that received combination therapy than in the group on megestrol acetate alone. Serum values of IL-6 and tumour necrosis factor decreased only in the combination therapy group, just as handgrip strength was only improved in this group.[27] Another small study[28] used a combination therapy of oral formoterol (80 μg/d) and megestrol acetate tablets (480 mg/d) for up to 8 weeks in 13 patients with advanced malignancy and involuntary weight loss. Six of 7 patients who completed the study showed an improvement in muscle size and muscle function as assessed using quadriceps strength and magnetic resonance imaging. In fact, quadriceps volume increased significantly ($P < .02$); in addition, there was a trend toward an increase in the patients' quadriceps and handgrip strength.[28]

Just as with thalidomide, several workers have tried to enhance the effects of megestrol acetate on appetite using different approaches. L-carnitine, for example, plays a central role in fatty acid metabolism and possesses antioxidant and anti-inflammatory properties.[29] Madeddu et al[30] randomized 60 patients with advanced cancer at any site and weight loss of at least 5% to receive either L-carnitine 4 g per day plus celecoxib 300 mg per day or the same regimen plus megestrol acetate 320 mg per day. After 4 months of treatment, no significant difference was noted between the 2 treatments with regard to an increase in lean body mass, total daily physical activity, handgrip strength, or 6-minute walk distance. However, when the 2 arms were analyzed separately, significant increases were noted in each arm for lean body mass (by about 2.5 kg, both $P < .04$) and 6-minute walk distance (approximately 50 m, both $P < .04$). No change was noted for physical activity or grip strength. Resting energy expenditure decreased significantly in both groups. Body weight was increased in the group that received megestrol acetate only (from 54.7 ± 10.8 to 57.2 ± 11.8 kg, $P = .05$).

L-carnitine on its own also has been successfully used in 72 patients with advanced pancreatic cancer as part of a prospective, multicenter, placebo-controlled, randomized, and double-blinded trial.[31] Patients received oral L-carnitine at a dose of 4 g or placebo. At study entry, patients reported a mean weight loss of 12.0 ± 2.5 kg. During 12 weeks of treatment, body mass index increased by 3.4% ± 1.4% under L-carnitine and decreased by 1.5% ± 1.4% in controls ($P < .05$). Likewise, body fat and body cell mass increased in the L-carnitine group only.

The appetite stimulant megestrol acetate also has been successfully used in children. Cuvelier et al[32] randomized, in a double-blind fashion, 26 children to receive an oral suspension of megestrol acetate (7.5 mg/kg/d) or placebo for 90 days. Patients enrolled into the study were younger than 18 years of age and presented with weight loss of 5% or more secondary to cancer and/or cancer treatment. Children on megestrol acetate experienced an average weight gain of +19.7% compared with a mean weight loss of 1.2% in the placebo group ($P = .003$).[32] All patients in the megestrol acetate group developed at least one undetectable early morning serum cortisol level during the study; this occurred only in 1 patient on placebo. Severe adrenal suppression was reported in 2 patients on megestrol acetate. Other adverse effects were not different between this and the placebo group.[32]

Melatonin has been shown to improve appetite in animal experiments.[33] Del Fabbro et al[34] performed a randomized, placebo-controlled trial in patients with advanced lung or gastrointestinal cancer. Unfortunately, the trial was stopped early for futility. This result came as a surprise, because the dosage used in this trial, oral melatonin 20 mg at night, was similar to that used in previous trials and is much higher than that used for conditions such as jet lag (typically 0.5–5.0 mg). A total of 73 patients were enrolled, but it was stopped after 48 subjects had finished the study, because an interim analysis showed that the intervention was unlikely to be of significant benefit. In fact, none of the assessed end points improved: the Edmonton Symptom Assessment Scale (ESAS), the Functional Assessment of Cancer Illness Therapy–Fatigue (FACIT-F), or the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) scores. Also, there was no change in body weight to suggest any benefit of melatonin over placebo (all $P > .15$).[34]

Inflammation

Inflammatory processes have been shown to maintain the wasting process in cachexia. Hong et al[35] used a novel approach to target inflammation and its consequences in patients with advanced cancer. For this purpose, they designed a dose-escalation and expansion approach using a first-in-class monoclonal antibody (MABp1) cloned from a human being that targets IL-1α. The first, dose-escalation part of the study identified an optimal intravenous dose of 3.75 mg/kg every 2 weeks. Using this dose, the following phase II study was performed. In the 42 patients in this open-label, uncontrolled study, median plasma IL-6 concentrations decreased from baseline to week 8 ($P = .08$). Of the 34 patients who were restaged, 1 patient had a partial response and 10 had stable disease. Among 30 patients with an assessment of body composition, lean mass increased significantly by 1.02 ± 2.24 kg ($P = .02$). Overall, the drug was well tolerated.[35]

Two recent interventional studies used thalidomide to treat cachexia. Unfortunately, thalidomide is a drug associated with tragedy, because a single dose can induce malformation of the unborn in pregnant women.[36] Despite these effects, it has been rediscovered for its anti-inflammatory properties, and reports dating back more than 20 years have demonstrated successful treatment of erythema nodosum leprosum.[37] Yennurajalingam et al[38] studied 31 patients with advanced cancer with weight loss of more than 5% in the previous 6 months who also reported anorexia and fatigue. Patients were, in a double-blinded fashion, randomized to receive 100 mg thalidomide daily (n = 15) or placebo for a comparatively short duration of 14 days. Only 21 patients completed the study. Statistically significant decreases were noted for fat mass (median: −1.5 kg, $P = .03$) and fat-free mass (−4.8 kg, $P = .024$) after 14 days of treatment with thalidomide. Some changes with regard to cytokine levels were noted as well; however, no effect was noted for the ESAS, FAACT, the FACIT-F, the Hospital Anxiety Depression Scale, or the Pittsburgh Sleep Quality Index. Another small phase II trial was conducted by Davis et al[39] using 50 mg of thalidomide administered orally at bedtime; however, this trial was uncontrolled and unblinded. Nonresponders

Table 1
Cachexia Intervention Trials Published Between 2012 and 2014

Reference	Study Design	Disease	No. of Patients*	Duration	Intervention Groups	Main Results
Appetite stimulation						
Wen et al 2012[27]	Single-center, randomized, controlled, open-label	Cancer with loss of 5% of body weight	102 (93)	8 wk	(1) Megestrol acetate 160 mg twice daily po plus thalidomide 50 mg twice daily po	Increases in body weight, quality of life, appetite, and grip strength.
					(2) Megestrol acetate 160 mg twice daily po	Increases in body weight and appetite.
Greig et al 2014[28]	Single-center, nonrandomized, uncontrolled, open-label	Cancer	13 (7)	8 wk	Formoterol 80 μg/d po plus megestrol acetate 480 mg/d po	Six responders with an increase in quadriceps volume; trend for increases in quadriceps and hand grip strength.
Maddedu et al 2012[30]	Single-center, randomized, controlled, open-label	Cancer with weight loss of 5%	60	4 mo	(1) L-carnitine 4 g/d po plus celecoxib 300 mg/d po	Increases in lean body mass and 6-minute walk distance. No significant difference between the 2 groups.
					(2) L-carnitine 4 g/d po plus celecoxib 300 mg/d po plus megestrol acetate 320 mg/d po	
Kraft et al 2012[31]	Multicenter, randomized, placebo-controlled, double-blind	Advanced pancreatic cancer	72 (26)	12 wk	(1) L-carnitine 4 g/d po	Weight gain due to increases in body cell mass and body fat.
					(2) Placebo	No effect.
Cuvelier et al 2014[32]	Single-center, randomized, placebo-controlled, double-blind	Cancer with weight loss ≥5%	26 children	90 d	(1) Megestrol acetate suspension 7.5 mg/kg/d po	Increases in body weight, body mass index, and mid upper arm circumference.
					(2) Placebo	Weight loss.
Del Fabbro et al 2013[34]	Single-center, randomized, placebo-controlled, double-blind	Cancer with weight loss ≥5%	73 (48)	28 d	(1) Melatonin 20 mg at bedtime po (2) Placebo	Terminated early for futility.
Inflammation						
Hong et al 2014[35]	Single-center, non-randomized, uncontrolled, open-label	Cancer	52 (42)	8 wk	Monoclonal anti-interleukin-1α antibody (MABp1) 3.75 mg/kg IV	Decrease in serum interleukin-6, increase lean body mass, partial response in 1 of 34, stable disease in 10 of 34 patients.
Yennurajalingam et al 2012[38]	Single-center, randomized, placebo-controlled, double-blind	Cancer with weight loss ≥5%	31 (21)	14 d	(1) Thalidomide 100 mg/d po	Decrease and fat mass and fat-free mass.
					(2) Placebo	No effect.
Davis et al 2012[39]	Single-center, nonrandomized, uncontrolled, open-label	Cancer	35 (33)	14 d	Thalidomide 50 mg po at bedtime, uptitrated to 100 or 200 mg po at bedtime in nonresponders	Improvments in appetite, insomnia, and quality of life.
Rattanasompattikul et al 2013[41]	Single-center, randomized, placebo-controlled, double-blind	Maintenance dialysis with hypoalbuminemia	93 (74)	16 wk	(1) One can of nutritional support plus 1 can of anti-inflammatory, antioxidant nutrition plus pentoxyphylline 400 mg 3 times weekly po	Significant increases in serum albumin levels.
					(2) One can of nutritional support plus 1 can of anti-inflammatory, antioxidant nutrition plus placebo	
					(3) Two cans of nutritional placebo plus pentoxyphylline 400 mg 3 times weekly po	
					(4) Two cans of nutritional placebo plus placebo tablet	No change.
Ghrelin						
Miki et al 2012[61]	Multicenter, randomized, placebo-controlled, double-blind	COPD and cachexia	33	3 wk	(1) Ghrelin 2 mg/kg IV twice daily	Increase in 6-minute walk distance after 7 wk.
					(2) Placebo	No effect after 7 wk.
Temel et al 2013[62]	Multicenter, randomized, placebo-controlled, double-blind	Cancer	226	12 wk	(1) Anamorelin 50 mg/d po	Weight loss.
					(2) Anamorelin 100 mg/d po	Weight gain.
					(3) Placebo	Weight loss.

Garcia et al 2013[64]	Multicenter, randomized, placebo-controlled, double-blind	Cancer	16	3 d	(1) Anamorelin 50 mg/d po (2) Placebo	Weight gain, increase in appetite. Weight loss.
Enobosarm and other anabolics						
Dobs et al 2013[74]	Multicenter, randomized, placebo-controlled, double-blind	Cancer with weight loss ≥2%	159 (100)	Up to 113 d	(1) Enobosarm 1 mg/d po (2) Enobosarm 3 mg/d po (3) Placebo	Increase in total lean mass and stair climb power. No effect.
Crawford et al 2014[75]	Multicenter, randomized, placebo-controlled, double-blind	Cancer	641	5 mo	(1) Enobosarm 3 mg/d po (2) Placebo	Increase in lean body mass. No effect.
Del Fabbro et al 2013[76]	Single-center, randomized, placebo-controlled, double-blind	Cancer	29	4 wk	(1) Injection of testosterone 150 or 200 mg every 14 d IM (2) Placebo	No significant effect on quality of life.
Stewart Coats et al 2014[80]	Multicenter, randomized, placebo-controlled, double-blind	Cancer with weight loss ≥5%	87	16 wk	(1) Espindolol 2.5 mg twice daily po (2) Espindolol 10 mg twice daily po (3) Placebo	Increase in hand grip strength. Increase in lean and fat mass and in hand grip strength. No effect.

IM, intramuscular; IV, intravenous; po, per os.
*Number of patients enrolled and, in parentheses, number of patients in final analysis.

with regard to appetite were uptitrated every 2 weeks to 100 mg, then to 200 mg once daily. Of 33 patients with active cancer and loss of appetite as assessed using a numerical rating scale, 64% showed improved appetite. In addition, patients' insomnia and quality of life categorical scale values increased significantly.

Wasting plays a major role not only in patients with cancer, but also in patients with chronic kidney disease.[40] Rattanasompattikul et al[41] randomized 93 patients on maintenance dialysis in a double-blind fashion to 1 of 4 groups, receiving either (1) 1 can of nutritional support and 1 can of an anti-inflammatory, antioxidant nutrition along with 1 tablet of pentoxyphylline (400 mg, 3 times weekly), which is known to possess anti-inflammatory properties as well; (2) 2 cans of active nutrition as described before plus a placebo tablet; (3) 2 cans of nutritional placebo plus a pentoxyphylline tablet; (4) 2 cans of nutritional placebo plus 1 placebo tablet. At inclusion, all patients had been hypoalbuminemic for at least the previous 3 months, defined as serum albumin values lower than 4 g/dL. After 16 weeks of treatment, significant increases in serum albumin were found after all 3 interventions, but not in the placebo group. None of the groups showed a significant decline in the inflammatory markers C-reactive protein, IL-1β, or IL-6.[41]

Ghrelin

Ghrelin is a 28-amino acid peptide hormone mostly produced in the stomach, but also in other gastrointestinal tissues.[11,42] It induces the release of growth hormone from the pituitary gland and stimulates food intake.[43,44] Ghrelin also inhibits the production of the proinflammatory cytokines IL-1α, IL-6, and tumor necrosis factor, but induces the anti-inflammatory cytokine IL-10.[45] Overall, the metabolic changes induced by ghrelin lead to an increase in body weight and body fat mass, but also in lean tissue mass, the latter possibly mediated by a reduction in myostatin plasma levels. Even though gender-specific differences have been reported in men and women,[46,47] overall ghrelin plasma levels have been shown to be decreased in obesity and elevated in cachexia. In addition, ghrelin has been suggested to link nutrition and reproduction, because animal experiments have shown that ghrelin administration leads to inhibitory responses in the secretion of luteinizing hormone and testosterone, thus potentially contributing to hypogonadism.[48]

Ghrelin administration has therapeutic appeal for its anabolic activities,[49] and ghrelin plasma levels have been assessed in several observational studies of cachexia in chronic diseases.[50–52] Ghrelin agonists, such as anamorelin, carry potential in the treatment of cachexia as they mimic a natural ligand for the growth hormone secretagogue receptor and thus stimulate food intake and appetite.[53] Starting in 2004, a small number of interventional studies have used oral, intravenous, or subcutaneous ghrelin administration[45] for the treatment of wasting in chronic heart failure,[54] COPD,[55] cancer,[56–58] or end-stage renal disease.[59,60] The most recent additions to the ghrelin intervention portfolio have been performed in COPD and cancer. Miki et al[61] performed a multicenter, randomized, double-blind, controlled trial including 33 cachectic patients with COPD who were randomly assigned to receive placebo or intravenous ghrelin at a dose of 2 mg/kg of body weight twice daily for 3 weeks. Patients on ghrelin treatment displayed an increase in their 6-minute walking distance after 3 weeks (placebo [m ± SE]: +35 ± 12 m vs ghrelin: +40 ± 17 m, both $P < .05$ vs baseline) that was maintained out to 7 weeks (placebo: +47 ± 17 m [$P < .05$ vs baseline] vs ghrelin: +18 ± 11 m). No change was noted in the patients' peak oxygen consumption value. Unfortunately, the beneficial findings on patients' 6-minute walk distance could not be pathophysiologically explained, as there were no changes noted in body weight, total lean mass, serum IL-6, tumor necrosis factor, or hand grip strength.

More promising results were obtained in a clinical trial in 226 patients with stage 3 or 4 non–small cell lung cancer who received anamorelin in an international, randomized, double-blind, 12-week phase II study.[62] Patients were randomized to placebo (n = 76) or oral anamorelin 50 mg (n = 76) or 100 mg (n = 73) per day. A beneficial effect on body weight was observed as early as 1 week after anamorelin treatment initiation. Over 12 weeks, the group that received 100 mg anamorelin gained on average 0.14 kg compared with baseline, whereas mean losses of 0.3 kg and 1.32 kg occurred in the 50-mg and placebo group ($P = .0005$). No effect was noted on hand-grip strength or survival. The larger ROMANA 2 phase III trial that included 495 patients with non–small cell lung cancer was recently finished, but results have not been reported so far.[63] Garcia et al[64] performed a multicenter, double-blind, placebo-controlled crossover trial that evaluated the effects of anamorelin in 16 cachectic patients with different cancers. Patients were randomly assigned to receive oral anamorelin at a dosage of 50 mg per day or placebo for 3 days. Compared with placebo, treatment with anamorelin induced significant increases in body weight (placebo: −0.33 kg vs anamorelin: + 0.77 kg, $P = .02$), appetite ($P < .02$), and serum levels of growth hormone and insulin-like growth factor-1.

Enobosarm and Other Anabolics

Anabolic steroids have been effectively used to treat muscle wasting[65,66]; for example, in chronic heart failure where almost 20% of patients are affected by this problem.[67] In patients with heart failure, low levels of circulating anabolic hormones are associated with poor outcomes.[68,69] The problem with the administration of anabolic steroids is that their risks often outweigh their potential benefits. Selective androgen receptor modulators (SARMs) belong to a relatively new class of therapeutics currently under development that possesses anabolic properties without adverse effects on prostate, skin, or hair, frequently associated with testosterone treatment.[70,71] Enobosarm, an orally bioavailable nonsteroidal SARM with tissue-specific anabolic and androgenic activity, has shown improvements in lean mass and physical function in healthy younger as well as in healthy elderly men and postmenopausal women.[72] The latter study was published in 2011, highlighting a large unmet clinical need.[1] Recently, collagen VI fragment has been suggested as a marker of anabolic response that could be useful in patients treated with SARMs.[73]

Dobs et al[74] conducted a randomized, double-blind, placebo-controlled phase II trial to assess the efficacy and safety of enobosarm in 159 male and postmenopausal female patients with cancer who had lost at least 2% of body weight in the 6 months before randomization. Patients were randomized to receive oral enobosarm at a dosage of 1 (n = 53) or 3 mg (n = 54) or placebo (n = 52) once daily for up to 113 days at centers in the United States or Argentina. The primary end point was defined as the change in total lean body mass from baseline as assessed by dual-energy X-ray absorptiometry (DEXA). After study termination, significant increases in total lean mass were noted in both enobosarm groups (enobosarm 1 mg: median 1.5 kg, range −2.1 to 12.6, $P = .001$ vs baseline, enobosarm 3 mg: 1.0 kg, −4.8 to 11.5, $P = .046$). The study drug was well tolerated. POWER (Prevention and treatment Of muscle Wasting in patients with cancER) was a double-blind, randomized, placebo-controlled phase III trial of enobosarm 3 mg once daily that aimed to assess lean body mass and physical function after treatment. Preliminary results were recently presented in abstract form.[75] A total of 641 patients with stage 3 or 4 non–small cell lung cancer were randomized into 1 of 2 trials at initiation of first-line chemotherapy (platinum plus taxane or platinum plus nontaxane) plus add-on, consisting of either enobosarm or placebo for 5 months. The study's coprimary end points, as assessed after 84 days of treatment, were physical function response assessed by stair-climb power and lean body mass as measured by DEXA. Compared with placebo, enobosarm treatment was associated with an increase in the stair-climb power and the lean body mass in the platinum plus taxane treatment arm, whereas in the platinum plus nontaxane arm, there was only a significant increase in the patients' lean body mass (all $P < .02$).

Using intramuscular testosterone replacement, Del Fabbro et al[76] performed a randomized, double-blind, placebo-controlled trial in 29 patients with advanced cancer, low bioavailable testosterone, and a fatigue score higher than 3 of 10 on the ESAS. Unfortunately, 4 weeks of treatment did not change patients' FACIT score values in the testosterone group (n = 13, administered every 2 weeks) as compared with the placebo group (n = 16). Improvements were noted in the testosterone group with regard to the Sexual Desire Inventory score ($P = .05$) and the patients' performance status ($P = .02$). The authors therefore concluded that "four weeks of intramuscular testosterone replacement in hypogonadal male patients with advanced cancer did not significantly improve quality of life."[76]

Another novel anabolic agent has recently been tested in a randomized, double-blind, controlled trial. MT-102, also known as espindolol, is a novel anabolic/catabolic transforming agent that appears to possess 3 potential pharmacological targets in cancer cachexia: (1) reduced catabolism through nonselective β-blockade, (2) reduced fatigue and thermogenesis through central 5-HT1a antagonism, and (3) increased anabolism through partial β-2 receptor agonism.[77] Animal experiments in 19-month-old male Wistar Han rats have shown that espindolol can abolish the effects of aging-associated body and muscle wasting.[78] Indeed, although placebo-treated animals progressively lost body weight, lean and fat mass, espindolol-treated animals showed increases in all these parameters without affecting cardiac function. Key regulators of muscle catabolism showed reduced expression under espindolol treatment. Another animal study showed that the beneficial effects of espindolol on wasting were more pronounced than those of other beta-blockers.[79] The ACT-ONE trial was designed to test whether MT-102 (espindolol) will positively impact the rate of change of body weight in cancer cachexia. The trial's preliminary results were recently published in abstract form.[80,81] It enrolled a total of 87 patients with non–small cell lung cancer or colorectal cancer from 17 centers who were in stage 3 or 4 of the disease. Patients were randomized in a 3:1:2 fashion to 1 of 2 doses of espindolol (10.0 or 2.5 mg twice daily) or placebo and treated for 16 weeks. Only the higher dose of espindolol improved lean and fat mass. Hand grip strength increased significantly after 16 weeks in the low-dose and high-dose treatment groups, but stair climbing power and 6-minute walking distance did not.

Conclusions

Muscle wasting and cachexia remain great challenges in clinical practice. Clinical trials in this field remain small, and most are undertaken in oncology patients. Much research has focused on appetite stimulation (mostly using megestrol acetate), anti-inflammatory pathways, and anabolics. Ghrelin has shown some potential in clinical trials as has enobosarm. Results of the POWER trial with enobosarm, one of the few large-scale trials to improve muscle mass and function in patients with advanced cancer, are eagerly awaited. In addition, results of the ACT-ONE trial using the anabolic/catabolic transforming agent espindolol have shown promising results.

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