J Cachexia Sarcopenia Muscle (2011) 2:121–123
DOI 10.1007/s13539-011-0040-8

EDITORIAL

Breakthrough in cachexia treatment through a novel selective androgen receptor modulator?!

Thomas Thum · Jochen Springer

Received: 19 August 2011 / Accepted: 26 August 2011

Abstract Cachexia, and particularly the loss of metabolically active lean tissue, leads to increased morbidity and mortality in affected patients. An impairment of strength and functional status is usually associated with cachexia. A variety of anabolic and appetite-stimulating agents have been studied in patients with cachexia caused by various underlying diseases. Overall, these studies have demonstrated that treatment can increase body weight and/or lean body mass. However, these therapies may have severe side effects, particularly when utilizing testosterone and related anabolic steroids targeting the androgen receptor. These side effects include cardiovascular problems, prostate hyperplasia and cancer in men, as well as virilization in women.

T. Thum (✉)
Institute of Molecular and Translational Therapeutic Strategies (IMTTS), IFB-Tx, Hannover Medical School,
Carl-Neuberg-Str. 1,
30625 Hannover, Germany
e-mail: thum.thomas@mh-hannover.de

T. Thum
Centre for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy

J. Springer
Applied Cachexia Research, Department of Cardiology, Charité Campus Virchow-Klinikum,
Berlin, Germany

J. Springer
Center for Cardiovascular Research, Charite Medical School,
Berlin, Germany

J. Springer
Norwich Medical School, University of East Anglia,
Norwich, UK

Cachexia is defined as a multidimensional syndrome including ongoing loss of skeletal muscle mass that withstands full reversion by conventional nutritional support leading to progressive functional impairment [1]. The development of cachexia goes through various stages, that is pre-cachexia to cachexia to refractory cachexia and can develop due to many various diseases including cancer, heart and lung diseases, or other diseases ([2–4] for excellent overviews). In the past, many drugs were developed with anabolic properties with the intention to "cure" cachectic states but many had limited success and broad unwanted side effects. For instance, the armada of anti-cachectic drugs includes appetite stimulants, androgens, and growth factors (see Table 1). Mechanistically, androgen receptor modulators were of particular interest. Testosterone is converted in peripheral tissues by the enzyme 5[alpha]-reductase to 5[alpha]-dihydrotestosterone (DHT). Both testosterone and DHT are able to activate the androgen receptor resulting in an array of anabolic effects on the whole body including heart, liver, bone, and skeletal muscle [5, 6]. Of concern are the increased risks for prostate hyperplasia and cancer in men, virilization in women, and cardiovascular side effects such as cardiac hypertrophy and atherosclerosis. Therefore, nonsteroidal selective androgen receptor modulators (SARMs) have been developed with preferential effects on muscle and bone, and less side effects [7].

In the current issue of the *Journal of Cachexia, Sarcopenia and Muscle*, Dalton and colleagues report a 12-week randomized, double-blind, placebo-controlled multicenter trial, where effects of GTx-024 (enobosarm), an orally available nonsteroidal SARM with tissue-selective anabolic activity have been tested in 120 healthy elderly men [8]. GTx-024 treatment significantly increased total lean body mass and improved physical function as well as insulin resistance. No increased adverse effects were observed when compared to placebo treatment. This is an exciting trial with numerous implications for future cachexia treatment strategies.

Table 1 Currently used anti-cachectic treatments

Drug	Effect/approved	Adverse effects	Reference
Megace	Appetite stimulant Approved for AIDS cachexia	Hypogonadism, adrenal suppression, deep venous thrombosis, hyperglycemia	[10–12]
Dronabinol	Appetite stimulant Approved for AIDS cachexia	Euphoria, dizziness	[13]
Testosterone	Increase in weight and lean body mass	Prostate hyperplasia and cancer in men, virilization in women	[14, 15]
DHT	Increase in weight and lean body mass	Prostate hyperplasia and cancer in men, virilization in women	[16, 17]
Nandrolone	Increased lean body mass Approved in CKD	Peripheral edema, arthralgia, decreased total testosterone, and HDL cholesterol levels, increased hemoglobin and hematocrit	[18]
Oxandrolone	Approved as short term treatment for weight loss	Transient elevations in transaminase levels, reduction in HDL cholesterol	[19, 20]
Oxymetholone	Approved for anemia treatment	Elevations in liver enzymes	[20]
Growth hormone/IGF-1	Protein synthesis	Arthralgia, myalgia, puffiness, diarrhea	[20, 21]

DHT 5[alpha]-dihydrotestosterone

Of importance, the tissue-specific effects were proven by the significant dose-dependent increase in lean body mass and loss of free fat. The increase in muscle mass and decrease in fat may be one explanation for the observed increase in physical strength in GTx-024-treated individuals. The reason why here no dose-dependent effect was seen and only the highest dose (3.0 mg) resulted in significant improvements is not clear, and although the used stair climb power test is useful as a general test for muscle strength, effects on physical activity needs to be measured with broader techniques. In addition, spiroergometric assessment of physical endurance would be helpful to assess GTx-024 effects on endurance.

Several other issues in the current study are worthy to note and to be considered in future trials with this compound. With respect to the patient characteristics, it is not clear why the body mass index (BMI) of the placebo and 0.1, 0.3, and 1.0 mg dose groups was between 24 and 26 kg/m², whereas that of the 3.0 mg dose group, it was considerably less (21.35 kg/m²). As significant improvements, especially for %change in lean body mass and physical activity were only found in the highest 3.0 mg dose group, the differences in baseline BMI may partially contribute to those effects, and therefore, future trials need to balance baseline BMI more carefully.

The effects of GTx-024 on decreased blood glucose and insulin resistance are remarkable and may be beneficial in cachectic patients and diabetes. On the other hand, great care is needed when this drug is co-administered with anti-diabetic drugs including oral anti-diabetics and insulin with respect to glucose control.

Although the overall cholesterol/HDL ratio was basically unaffected by GTx-024, the general HDL decrease is still of some concern as this is a proof that there are still (unwanted) side (and not tissue-selective) effects of this novel non-steroidal selective androgen modulator. Likewise, the increase in overall hemoglobin levels should not be overseen. This may be beneficial in cachectic patients as most suffer from anemia, but the underlying reasons should be further investigated.

Currently, we still wait for clinically accepted and approved therapies for the prevention of and treatment of muscle wasting. This relatively large multicenter clinical trial may be a major breakthrough although still questions about tissue selectivity, side effects, and long-term safety are unanswered. We also do not know whether the effects in healthy elderly men will be seen in the wanted target populations of cachectic patients due to alterations in liver metabolism, kidney function, and so on. However, this compound seems to be a significant milestone in SARM development and, thus, a strong candidate for further clinical studies.

Acknowledgments The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle* [9]. The authors thank Yvonne Görzig for the editorial help. The kind research support of the BMBF (IFB-Tx; 01EO0802 to TT) is acknowledged.

References

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12:489–95.
2. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle. 2010;1:1–5.

3. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. J Cachexia Sarcopenia Muscle. 2011;2:9–25.
4. von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. Pharmacol Ther. 2009;121:227–52.
5. Lee NK, MacLean HE. Polyamines, androgens, and skeletal muscle hypertrophy. J Cell Physiol. 2011;226:1453–60.
6. Dillon EL, Durham WJ, Urban RJ, Sheffield-Moore M. Hormone treatment and muscle anabolism during aging: androgens. Clin Nutr. 2010;29:697–700.
7. Schmidt A, Harada S, Kimmel DB, Bai C, Chen F, Rutledge SJ, et al. Identification of anabolic selective androgen receptor modulators with reduced activities in reproductive tissues and sebaceous glands. J Biol Chem. 2009;284:36367–76.
8. Dalton JT, Barnette KG, Bohl CE, Hancock ML, Rodriguez D, Dodson ST, Morton RA, Steiner MS. The selective androgen receptor modulator, GTx-024 (enobosarm), improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. J Cachexia Sarcopenia Muscle. 2011. doi:10.1007/s13539-011-0034-6.
9. von Haehling S, Morley JE, Coats AJ, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle. J Cachexia Sarcopenia Muscle. 2010;1:7–8.
10. Pascual Lopez A, Roque i Figuls M, Urrutia Cuchi G, Berenstein EG, Almenar Pasies B, Balcells Alegre M, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. J Pain Symptom Manage. 2004;27:360–9.
11. Caparros GC, Zambrana JL, Delgado-Fernandez M, Diez F. Megestrol-induced Cushing syndrome. Ann Pharmacother. 2001;35:1208–10.
12. Koller E, Gibert C, Green L, Mann M, Bernstein B. Thrombotic events associated with megestrol acetate in patients with AIDS cachexia. Nutrition. 1999;15:294–8.
13. Yeh SS, Lovitt S, Schuster MW. Pharmacological treatment of geriatric cachexia: evidence and safety in perspective. J Am Med Dir Assoc. 2007;8:363–77.
14. Vigano A, Piccioni M, Trutschnigg B, Hornby L, Chaudhury P, Kilgour R. Male hypogonadism associated with advanced cancer: a systematic review. Lancet Oncol. 2010;11:679–84.
15. Ho CK, Habib FK. Estrogen and androgen signaling in the pathogenesis of BPH. Nat Rev Urol. 2011;8:29–41.
16. Unimed pharmaceuticals begins HIV wasting syndrome trial. J Int Assoc Physicians AIDS Care. 1996;2:51.
17. Haendler B, Cleve A. Recent developments in antiandrogens and selective androgen receptor modulators. Mol Cell Endocrinol. 2011. doi:10.1016/j.mce.2011.06.002.
18. Storer TW, Woodhouse LJ, Sattler F, Singh AB, Schroeder ET, Beck K, et al. A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. J Clin Endocrinol Metab. 2005;90:4474–82.
19. Orr R, Fiatarone Singh M. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. Drugs. 2004;64:725–50.
20. Mulligan K, Schambelan M. Anabolic treatment with GH, IGF-I, or anabolic steroids in patients with HIV-associated wasting. Int J Cardiol. 2002;85:151–9.
21. Gelato M, McNurlan M, Freedland E. Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. Clin Ther. 2007;29:2269–88.