HHS Public Access

Author manuscript

J Frailty Aging. Author manuscript; available in PMC 2018 July 10.

Published in final edited form as:

J Frailty Aging. 2015 ; 4(3): 121–122. doi:10.14283/jfa.2015.65.

SELECTIVE ANDROGEN RECEPTOR MODULATORS AS FUNCTION PROMOTING THERAPIES

S. BHASIN

Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Introduction

Despite empiric evidence that androgens promote muscle growth, concerns remain about their safety, particularly their association with prostate hypertrophy, the development of male secondary sex characteristics in women, and their potential to accelerate the development of prostate cancer. These concerns led to the development of selective androgen receptor modulators (SARMs), a class of androgen receptor ligands that bind to androgen receptors in a tissue-selective manner to activate of androgenic signaling (1). SARMs are used for many indications including osteoporosis, anemia, male contraception, male hypogonadism, and wound healing. SARMs may be either steroidal or non-steroidal.

Mechanistic basis of SARM selectivity

Analysis of the Structure:Activity relationships (SARs) of SARMs has led to the identification of compounds with different profiles, for example selectivity for different tissues, oral activity, and/or extended duration of action. For example, some SARMs are effective as inhibitors of luteinizing hormone and follicle stimulating hormone, and thus may have potential as male contraceptives; while others are effect in stimulating erythropoiesis and may have potential as treatments for anemia. Some have also been shown to improve bone mineral density, bone strength, and bone architecture in ovariectomized mice, suggesting their usefulness as a treatment for osteoporosis (2).

The mechanistic basis for tissue selectivity is not well understood, although a number of hypotheses have been proposed (3, 4). Non-steroidal SARMs do not undergo aromatization of 5-α-reductase, an enzyme present at high levels in the prostate but low levels in bone and muscle. Conformational differences induced by different SARM structures could also lead to associations with different co-activators. Another hypothesis posits that different structures activate different intracellular signaling cascades.

SARMs in clinical trials

Osteoporosis may be a particular attractive indication for SARM development because the pathway for drug approval has been well developed over the past 20 years, using bone

Corresponding author: Shalender Bhasin, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. SBHASIN@partners.org.

mineral density and serum and urine biomarkers of bone metabolism as endpoints. The pathway for approval of a drug to improve function in people with sarcopenia or other muscle wasting diseases is less clear. Nonetheless, a number of clinical trials have been conducted:

- The SARM LGD-4033 has been shown to increase bone mineral density, bone formation, and bone strength in preclinical models, leading to a small, 21-day randomized, placebo-controlled, ascending dose trial in healthy young men. The drug was well tolerated and showed significant dose-proportional gains in lean body mass and leg press strength (5).
- Another SARM, MK-773, has undergone phase 2 studies in both men and women. One trial included 170 women age 65 or older randomized to receive MK-0773 or placebo. Both groups also were treated with vitamin D and protein supplements. Results showed a significant increase in lean body mass from baseline to month 6 vs. placebo, but no difference in leg strength or other physical function measures. Subjects receiving the drug also experienced modest increases in transaminases and decreased HDL (6).
- Ostarine, also known as enobosarm, has undergone the most extensive clinical trials to date. In a phase 2a study, ostarine was shown to increase lean body mass and decrease fat mass, and to modestly improve the homeostatic model assessment (HOMA), a measure of insulin sensitivity (Dalton 2007 abstract from Endo meeting).
- A phase 2 randomized, double-blind, placebo-controlled trial of enobosarm in cancer cachexia tested two doses of drug in men and women with cancer over a 16-week study period. Results showed significant increases in lean body mass. Adverse events included malignant neoplasm progression, pneumonia, and febrile neutropenia, but these were not thought to be treatment-related (7).
- Another study of enobosarm, this one in patients with non-small cell lung cancer (NSCLC) indicated that the drug increased lean body mass, improved strength, and improved survival but did not meet its primary endpoints (unpublished). Enobosarm for the treatment of NSCLC had been designated for the Food and Drug Administration (FDA) Fast Track development program.

In contrast to these first-generation non-steroidal SARMs, testosterone and steroidal SARMs have demonstrated stronger effects on lean body mass, leg-press strength, skeletal muscle remodeling, and functional performance (8–12). Importantly the effects of androgens are augmented by concomitant exercise (13). Indeed, 80 years of empiric evidence from athletes taking androgen supplements has shown conclusively that very substantial gains in muscle mass, strength, and athletic performance can be induced by task-specific exercise such as hitting a baseball or sprinting.

Conclusions

While first-generation SARMs are safe and efficacious in increasing lean body mass and possibly strength and stair climbing power, the gains are modest in comparison to those

induced by androgens. More potent and selective SARMs are needed, including agents that are stronger agonists on muscle and antagonists on prostate. Safety issues also need to be further explored. First generation SARMs are neither aromatized nor 5-α reduced, which poses unknown potential for risk. Finally, functional exercise training may be necessary to translate the physiological benefits of SARMs into functional improvements.

New study designs are also needed, with endpoints that represent clinically meaningful improvements, including endpoints such as a reduction in falls, fractures, or disability. It is possible that demonstration of functional improvement simply requires longer study duration. Long term observational studies and consensus building across the field will be essential to move the regulatory process forward.

References

1. Negro-Vilar A. Selective androgen receptor modulators (SARMs): a novel approach to androgen therapy for the new millennium. The Journal of clinical endocrinology and metabolism. 1999; 84(10):3459–62. [PubMed: 10522980]
2. Miner JN, Chang W, Chapman MS, et al. An orally active selective androgen receptor modulator is efficacious on bone, muscle, and sex function with reduced impact on prostate. Endocrinology. 2007; 148(1):363–73. [PubMed: 17023534]
3. Bhasin S, Jasuja R. Selective androgen receptor modulators as function promoting therapies. Curr Opin Clin Nutr Metab Care. 2009; 12(3):232–40. [PubMed: 19357508]
4. Narayanan R, Mohler ML, Bohl CE, Miller DD, Dalton JT. Selective androgen receptor modulators in preclinical and clinical development. Nucl Recept Signal. 2008; 6:e010. [PubMed: 19079612]
5. Basaria S, Collins L, Dillon EL, et al. The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. J Gerontol A Biol Sci Med Sci. 2013; 68(1):87–95. [PubMed: 22459616]
6. Papanicolaou DA, Ather SN, Zhu H, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013; 17(6):533–43. [PubMed: 23732550]
7. Dobs AS, Boccia RV, Croot CC, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: a double-blind, randomised controlled phase 2 trial. Lancet Oncol. 2013; 14(4):335–45. [PubMed: 23499390]
8. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med. 2010; 363(2):109–22. [PubMed: 20592293]
9. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. The Journal of clinical endocrinology and metabolism. 2006; 91(6):1995–2010. [PubMed: 16720669]
10. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. The Journal of clinical endocrinology and metabolism. 1999; 84(6): 1966–72. [PubMed: 10372695]
11. Storer TW, Woodhouse L, Magliano L, et al. Changes in muscle mass, muscle strength, and power but not physical function are related to testosterone dose in healthy older men. J Am Geriatr Soc. 2008; 56(11):1991–9. [PubMed: 18795988]
12. Travison TG, Basaria S, Storer TW, et al. Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. J Gerontol A Biol Sci Med Sci. 2011; 66(10):1090–9. [PubMed: 21697501]
13. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med. 1996; 335(1):1–7. [PubMed: 8637535]