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Perspective Article

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Novel, non-steroidal, selective androgen receptor modulators (SARMs) with anabolic activity in bone and muscle and improved safety profile

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Abstract

A novel approach to the treatment of osteoporosis in men, and possibly women, is the development of selective androgen receptor modulators (SARMs) that can stimulate formation of new bone with substantially diminished proliferative activity in the prostate, as well as reduced virilizing activity in women. Over the last several years, we have developed a program to discover and develop novel, non-steroidal, orally-active selective androgen receptor modulators (SARMs) that provide improved therapeutic benefits and reduce risk and side effects. In recent studies, we have used a skeletally mature orchiectomized (ORX) male rat as an animal model of male hypogonadism for assessing the efficacy of LGD2226, a non-steroidal, non-aromatizable, and non-5alpha-reducible SARM. We assessed the activity of LGD2226 on bone turnover, bone mass and bone strength, and also evaluated the effects exerted on classic androgen-dependent targets, such as prostate, seminal vesicles and muscle. A substantial loss of bone density was observed in ORX animals, and this loss was prevented by SARMs, as well as standard androgens. Biochemical markers of bone turnover revealed an early increase of bone resorption in androgen-deficient rats that was repressed in ORX animals treated with the oral SARM, LGD2226, during a 4-month treatment period. Differences in architectural properties and bone strength were detected by histomorphometric and mechanical analyses, demonstrating beneficial effects of LGD2226 on bone quality in androgen-deficient rats. Histomorphometric analysis of cortical bone revealed distinct anabolic activity of LGD2226 in periosteal bone. LGD2226 was able to prevent bone loss and maintain bone quality in ORX rats by stimulating bone formation, while also inhibiting bone turnover. LGD2226 also exerted anabolic activity on the levator ani muscle. Taken together, these results suggest that orally-active, non-steroidal SARMs may be useful therapeutics for both muscle and bone in elderly hypogonadal men through their anabolic activities. Since SARMs both prevent bone loss, and also stimulate formation of new bone, they may have significant advantages relative to currently used anti-resorptive therapies. Coupled with their activity in muscle and their ability to maintain or restore libido, they offer new therapeutic approaches for male and female hormone replacement.

Keywords: SARMs, Anabolic, Prostate Sparing, Bone Anabolic, Muscle Anabolic, Male Osteoporosis, Female Osteoporosis

Androgen therapy using injectable, oral and, more recently, transdermal preparations has been available for many years to physicians to treat a variety of male disorders and, to a lesser degree, their use has been extended to some female indications. The extent of use of androgen therapy, however, has not been widespread, unlike that of female sex hormones that have found extensive use and applications in the fields of hormone replacement, reproductive disorders, gynecological cancers and contraception[1].

Recent advances clearly indicate that androgen therapy is about to experience a fundamental change, both in terms of extent of use and in terms of the range of applications that may benefit from these upcoming advances[2]. Several factors have and will continue to contribute to this change. First, the significant advances brought by hormone replacement therapy (HRT) in postmenopausal females, and the expansion and application of HRT to treat and prevent major disorders such as osteoporosis, cardiovascular disease, breast cancer, mood and cognition, among others, have clearly established the need and utility of novel HRT therapies to improve women's health[3-5] and by extrapolation clearly point out the

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potential for similar approaches to address men's health disorders. Second, the development and marketing of novel selective estrogen receptor modulators (SERMS) has provided both pre-clinical and clinical proof-of-concept that we can develop molecules with a great degree of tissue selectivity targeting the estrogen receptor to eliminate undesired side effects and maintain (and in the future enhance) the positive, protective effects resulting from selective transcriptional receptor activation[4-8]. Third, significant advances in our understanding of nuclear receptor activation and function provided the molecular underpinnings to mount new drug development efforts to design and bring forward a new generation of tissue-selective molecules targeting steroid and other nuclear receptors. Proof-of-concept for tissue selectivity has now been extended to many compounds interacting with different nuclear receptors, such as the estrogen (ER), progesterone (PR), androgen (AR), retinoid (PAR/PXR), and peroxisome proliferation activated receptors (PPARs) among others[7-12].

Molecular advances in androgen receptor structure and function: A key to unlock tissue selectivity

The adrogen receptor is a transcription factor and a member of the extended family of nuclear receptors. As such, it shares significant homology in terms of structure with the other members of the family, including specific protein subdomains that either activate or repress gene activity. Current evidence indicates that these activation domains represent surfaces in the receptor that are induced or exposed upon hormone or ligand-binding in such a manner that it facilitates the interaction of the specific domain or surface with selected proteins named coactivators or corepressors[6,13]. These proteins are part of an expanding family of molecules and several of these have been found to bind directly to AR, namely CBP/p300[14], GRIP1[15], ARA54[16] and ARA55[17] and 70[16,17] and Tip 60[18]. Each selective ligand upon binding to the receptor may drive it into a distinct conformation that exposes activation or interaction surfaces resulting in recruitment of specific cofactors as revealed by structural studies[13].

Role of SARMs in androgen therapy for men

Currently used androgenic formulations for replacement therapy are largely restricted to injectable or skin delivery formulations of testosterone or testosterone esters.

The discovery and development of SARMs provides the opportunity to design molecules that are not only orally active, but that target the AR in different tissues to elicit the desired activity for each of the key indications benefiting from androgen therapy. We envision that an ideal SARM for the treatment of primary or secondary male hypogonadism would have the following profile: orally active, ideally with a PK consistent with once a day administration, capable of stimulating prostate, seminal vesicles and other sex accessory tissues at doses equipotent to those needed to provide increases in muscle mass and strength and fat-free mass, support bone growth and maintain/restore libido, virilization and male habitus. Unlike testosterone, which when converted to DHT in the prostate has an enhanced proliferative activity in relation to other peripheral tissues, these SARMs are not substrates for 5α reductase activity, nor do they affect the activity of the enzyme. Other activities that are considered undesirable should be diminished or eliminated, such as potential liver toxicity, blood pressure effects and fluid retention, induction of gynecomastia and overstimulation of erythropoiesis. On the other hand, use of SARMs for selected indications provides the rationale for developing molecules with distinct tissue specificity. For example, if the target is bone growth in elderly men with osteopenia or osteoporosis, but with no overt signs of hypogonadism, a more anabolic SARM with clear effects on bone and muscle, but lesser activity in the prostate or other sex accessory tissues would be more desirable.

SARMs for the treatment of osteoporosis

A novel approach to the treatment of osteoporosis in men, and possibly women, is the development of selective androgen receptor modulators (SARMs) that can stimulate formation of new bone with substantially diminished proliferative activity in the prostate, as well as reduced virilizing activity in women[22]. Over the last several years, we have developed a program to discover and develop novel, non-steroidal, orally-active selective androgen receptor modulators (SARMs) that provide improved therapeutic benefits and reduce risk and side effects. In recent studies, we have used a skeletally mature orchiectomized (ORX) male rat as an animal model of male hypogonadism for assessing the efficacy of LGD2226, a non-steroidal, non-aromatizable, and non-5alpha-reducible SARM. We assessed the activity of LGD2226 on bone turnover, bone mass and bone strength, and also evaluated the effects exerted on classic androgen-dependent targets, such as prostate, seminal vesicles and muscle. A substantial loss of bone density was observed in ORX animals, and this loss was prevented by SARMs, as well as standard androgens. Biochemical markers of bone turnover revealed an early increase of bone resorption in androgen-deficient rats that was repressed in ORX animals treated with the oral SARM, LGD2226, during a 4-month treatment period. Differences in architectural properties and bone strength were detected by histomorphometric and mechanical analyses, demonstrating beneficial effects of LGD2226 on bone quality in androgen-deficient rats. Histomorphometric analysis of cortical bone revealed distinct anabolic activity of LGD2226 in periosteal bone. LGD2226 was able to prevent bone loss and maintain bone quality in ORX rats by stimulating bone formation, while also inhibiting bone turnover. LGD2226 also exerted anabolic activity on the levator ani muscle. Taken together,

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