Selective androgen receptor modulators: the future of androgen therapy?

Andrew R. Christiansen¹, Larry I. Lipshultz²,³, James M. Hotaling⁴, Alexander W. Pastuszak⁴

¹University of Utah School of Medicine, Salt Lake City, UT, USA; ²Scott Department of Urology; ³Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA; ⁴Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA

Contributions: (I) Conception and design: AR Christiansen; (II) Administrative support: AW Pastuszak; (III) Provision of study material or patients: AR Christiansen; (IV) Collection and assembly of data: AR Christiansen; (V) Data analysis and interpretation: AR Christiansen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Alexander W. Pastuszak, MD, PhD. Assistant Professor, Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA. Email: alexander.pastuszak@hsc.utah.edu.

Abstract: Selective androgen receptor modulators (SARMs) are small molecule drugs that function as either androgen receptor (AR) agonists or antagonists. Variability in AR regulatory proteins in target tissues permits SARMs to selectively elicit anabolic benefits while eschewing the pitfalls of traditional androgen therapy. SARMs have few side effects and excellent oral and transdermal bioavailability and may, therefore, represent viable alternatives to current androgen therapies. SARMs have been studied as possible therapies for many conditions, including osteoporosis, Alzheimer's disease, breast cancer, stress urinary incontinence (SUI), prostate cancer (PCa), benign prostate hyperplasia (BPH), male contraception, hypogonadism, Duchenne muscular dystrophy (DMD), and sarcopenia/muscle wasting/cancer cachexia. While there are no indications for SARMs currently approved by the Food and Drug Administration (FDA), many potential applications are still being explored, and results are promising. In this review, we examine the literature assessing the use of SARMs for a number of indications.

Keywords: Androgen receptor (AR); androgen therapy; selective androgen receptor modulator (SARM)

Submitted Sep 13, 2019. Accepted for publication Oct 31, 2019.
doi: 10.21037/tau.2019.11.02

View this article at: http://dx.doi.org/10.21037/tau.2019.11.02

SARMs: history and mechanisms

Since their discovery near the close of the 20th century (1), selective androgen receptor modulators (SARMs) have been heralded as the possible future of androgen therapy (2). As satisfaction, side effects, preparations, and perceptions have limited the utility of testosterone therapy (TTh), SARMs are poised to fundamentally alter the field of androgen therapy (2).

SARMs are chemically engineered small molecule drugs that can selectively exert varying degrees of agonist and antagonist effects on the androgen receptor (AR) throughout the body. Like androgens, SARMs enter the cytoplasm and bind to the AR. After translocating to the nucleus, the SARM-AR complex acts as a transcriptional regulator and recruits cofactors and coregulatory proteins, modulating the transcriptional response to binding of the AR complex (3,4). While the AR is universally expressed, SARM-AR complexes can have varied effects due to variable cofactor recruitment (5). These complex configurations, along with tissue-dependent differences in AR expression patterns and regulatory milieu, allow for immense diversity of actions (4).

SARMs promise novel, convenient therapies that facilitate tissue-specific benefits without off-target side effects (6). Given the myriad drawbacks of TTh that can limit its use, including currently available formulations and common adverse effects, one can understand the excitement surrounding SARMs. Although still in the early stages of
clinical evaluation, SARMs may one day be used in the treatment of hypogonadism in a form that is orally active with convenient dosing frequency, and that can provide the beneficial effects of TTh without the adverse effects (2).

In addition to their potential use for the treatment of hypogonadism (7,8), SARMs are being explored as a potential therapy for osteopenia/osteoporosis (9-14), Alzheimer’s disease (15), prostate cancer (PCa) (16,17), benign prostatic hyperplasia (BPH) (18), male contraception (19), breast cancer (20), stress-induced urinary incontinence (21), sarcopenia (22), muscular dystrophy (23,24), and even cancer and chronic disease-related cachexia (25-30). While SARMs present an opportunity for therapy in several debilitating conditions, recent doubts concerning their ability to meet expectations have surfaced, especially concerning their utility in the treatment of cachexia.

Despite their potential to address significant unmet medical needs, regulatory roadblocks and poorly defined clinical study endpoints have tempered interest in the potential of SARMs for the first time since their discovery. Indeed, some now refer to the once-promising pathway to approval of SARMs as a “long and winding” one (31). More recently, the focus of using SARMs for cachexia has shifted to other clinical applications. The present review provides an overview of the developments in the literature and clinical trials on SARMs and offers a glimpse into the future therapeutic potential for SARMs.

Methods

A literature review was performed in the PubMed/Medline and ScienceDirect databases using the terms selective AR modulator, selective AR modulators, SARM, and SARMs. The initial search for literature resulted in 764 results. A total of 43 non-English language papers have been excluded. The remaining articles were screened for relevance and 97 were selected for inclusion in the review. Both basic and clinical studies have been included. Ongoing and recently concluded clinical trials listed on http://www.clinicaltrials.gov that are investigating SARMs were also reviewed and are compiled in Table 1.

The AR & SARMs

The AR, a nuclear steroid hormone receptor and transcription factor, is found in both reproductive and nonreproductive tissues of the human body. However, while the AR itself is widely expressed throughout the human body, the cofactors required for modulation of AR activity are not. The variability in expression of these coregulatory components is complex and allows for tissue-specific, targeted therapeutic effects (5). The mechanisms of how SARM-AR complex activity and coregulation function to modulate gene expression and physiologic effects remain to be elucidated. The AR is essential both for its role in male sexual development and maintenance but also has the potential to alter bone density, strength, muscle mass, hematopoiesis, coagulation, metabolism, and cognition (26,27). The complex regulatory environment of the AR allows selective receptor modulators (SRMs) to act as either agonists or antagonists, depending on the tissue and the expression of cofactors (3,32).

The first class of SRMs to be discovered was Selective Estrogen Receptor Modulators (SERMs) (33), which are best known for their use in breast cancer treatment (tamoxifen). The successful development of SERMs charted a course for the manipulation of nuclear receptor signaling in both men and women, and has been followed by the discovery of SARMs (1), Selective Progesterone Receptor Modulators (SPRMs) (34), Selective Glucocorticoid Receptor Modulators (SGRMs) (35), Farnesoid X receptor modulators (36), and others.

Tissue selectivity is a critical distinction between classic steroid hormone therapy and AR modulation. While TTh offers benefits including gains in muscle mass and strength, it is associated with a high rate of adverse effects, partly due to off-target activation of AR in several tissues (4), and TTh currently lacks a highly effective oral formulation. TTh has also been associated with risks including testicular atrophy, erythrocytosis, dyslipidemia, gynecomastia, hepatotoxicity, and, in women, virilization and uterine hyperproliferation (32,37,38). Meanwhile, SRMs/SARMs target AR function in specific tissues and cell types while minimizing effects on non-target tissues (6).

SARMs can be administered orally or transdermally (8), are mostly non-steroidal, and are capable of activating the AR in both muscle and bone. However, because they are not metabolized to dihydrotestosterone (DHT) by 5'-reductase, the risk of androgenic effects is reduced (27,38). In addition, SARMs are not metabolized to estrogen by aromatase, limiting estrogenic effects (30). While the benefits of first-generation SARMs appear modest compared to those of androgens (39), the ability of SARMs to preferentially stimulate bone and muscle growth, shrink the prostate, and inhibit breast cancer growth without significant systemic
Table 1 SARMs in recent clinical trials

<table>
<thead>
<tr>
<th>Study title</th>
<th>Clinical trials identifier</th>
<th>Phase</th>
<th>Intervention</th>
<th>Patient population</th>
<th>Primary outcome</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and Safety of GTx-024 in Patients With ER+/AR+ Breast Cancer</td>
<td>NCT02463032</td>
<td>Phase II</td>
<td>GTx-024 9 mg vs. GTx-024 18 mg</td>
<td>Postmenopausal Women with Metastatic or Locally Advanced ER+/AR+ Breast Cancer (BC)</td>
<td>Clinical benefit rate in centrally confirmed AR+ subjects</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Add-on Study for Protocol G200802 (NCT02463032): Effect of GTx-024 on Maximal Neuromuscular Function and Lean Body Mass</td>
<td>NCT02746328</td>
<td>Phase II</td>
<td>GTx-024 9 mg vs. GTx-024 18 mg</td>
<td>Postmenopausal Women age 18–70 with Metastatic or Locally Advanced ER+/AR+ Breast Cancer (BC)</td>
<td>Maximal Power Production (assessed by inertial-load cycle ergometry)</td>
<td>Completed</td>
</tr>
<tr>
<td>Pembrolizumab and Enobosarm in Treating Patients with Androgen Receptor-Positive Metastatic Triple-Negative Breast Cancer</td>
<td>NCT02971761</td>
<td>Phase II</td>
<td>Enobosarm + Pembrolizumab</td>
<td>Patients with metastatic triple-negative breast cancer</td>
<td>Safety and tolerability of treatment, the response rate</td>
<td>Recruiting; Estimated Primary Completion Date October 2019</td>
</tr>
<tr>
<td>Enobosarm and Anastrozole in Premenopausal Women with High Mammographic Breast Density</td>
<td>NCT03264651</td>
<td>Phase I</td>
<td>Enobosarm + Anastrozole</td>
<td>Premenopausal women aged 18–55 with high breast density and breast pain</td>
<td>Mammographic breast density, Breast tissue elasticity</td>
<td>Completed</td>
</tr>
<tr>
<td>Study to Assess Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence (ASTRID)</td>
<td>NCT03241342</td>
<td>Phase II</td>
<td>Enobosarm vs. Placebo</td>
<td>Post-menopausal women aged 18–80 with stress urinary incontinence</td>
<td>Change in number of stress urinary incontinence episodes</td>
<td>Completed</td>
</tr>
<tr>
<td>A Selective Androgen Receptor Modulator for Symptom Management in Prostate Cancer</td>
<td>NCT02499497</td>
<td>Phase II</td>
<td>LY2452473 vs. Placebo</td>
<td>Men aged 19 or older with a history of PCa</td>
<td>Harbor-UCLA 7-day Sexual Function Questionnaire</td>
<td>Recruiting; Estimated Primary Completion Date June 30, 2019</td>
</tr>
<tr>
<td>Effects and Safety of OPK-88004 Doses in Men with Signs and Symptoms of Benign Prostatic Hyperplasia (BPH)</td>
<td>NCT03297398</td>
<td>Phase II</td>
<td>OPK-88004 (15 or 25 mg) vs. Placebo</td>
<td>Men aged 45 or older with BPH-LUTS</td>
<td>Serum PSA</td>
<td>Terminated</td>
</tr>
<tr>
<td>Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of GSK2881078 in Single and Repeat Doses</td>
<td>NCT02045940</td>
<td>Phase I</td>
<td>GSK2881078 vs. Placebo</td>
<td>Healthy males aged 18–50</td>
<td>Safety and tolerability, pharmacokinetics, pharmacodynamics</td>
<td>Completed</td>
</tr>
<tr>
<td>Study to Evaluate the Safety and Efficacy of 13 Weeks of the Selective Androgen Receptor Modulator (SARM) GSK2881078 in Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>NCT03359473</td>
<td>Phase II</td>
<td>GSK2881078 vs. Placebo</td>
<td>Men and women aged 50–75 with COPD</td>
<td>Change in vitals, hematology, Active, not recruiting chemistry, urine parameters, number of adverse events, change in baseline in maximum leg press strength</td>
<td>Active, not recruiting</td>
</tr>
</tbody>
</table>
side effects is encouraging (40-46). Given that the treatment of many chronic diseases for which SARMs have been considered requires extended exposure, the apparent lack of significant adverse effects with SARMs as compared to androgens gives them a distinctive advantage.

Current and future clinical applications of SARMs

Osteoporosis

While existing therapies for osteoporosis are anti-resorptive, capable of halting bone breakdown but not reversing the process, multiple SARMs have demonstrated the ability to promote new bone growth and increase bone strength in animal models (9-13,47,48). Recently, four SARMs—BA321, YK11, ostarine, and LY305—have shown promise in the potential treatment of osteoporosis. These are listed in Table 2. BA321 can reverse bone loss without androgenic effects by binding to both AR and estrogen receptors (ER) in orchiectomized mice (13). Yatsu et al. described YK11, which can accelerate osteoblast cell proliferation via AR-mediated non-genomic activity (14). When mouse osteoblast cells (MC3T3-E1) were treated with YK11, it also promoted osteogenic activity, increased osteoblast-specific differentiation markers, and increased alkaline phosphatase (ALP) activity (a marker of osteoblast maturation) (14).

Hoffmann et al. investigated the bone-strengthening properties of ostarine (Enobosarm) in a rat model of postmenopausal osteoporosis (11). Eight weeks after ovariectomy, female rats were treated daily with low, intermediate, or high doses of ostarine for 5 weeks, with the low dose group showing no benefit, while the intermediate and high dose groups showing comparable improvements in microstructural indices including bone volume, density, and bone mineral density. These improvements were more significant in the femurs than in the vertebrae, although no significant improvements were observed in biomechanical properties (11).

In another study, LY305 reversed skeletal muscle atrophy and demonstrated increased bone formation in a bone fracture orchiectomized mouse model (8). LY305 was subsequently administered transdermally to humans in a phase I trial in order to circumvent high first-pass hepatic concentrations, which may contribute to dose-dependent suppression of high-density lipoprotein (HDL) observed with other oral SARMs (27,28). In this study by Krishnan et al., men who applied increasing doses of LY305 gel to the axilla or trunk daily for up to 4 weeks experienced minimal adverse effects and saw no change in HDL levels or hematocrit (8). Utilizing transdermal delivery to limit or prevent alterations in HDL is a significant step forward for the utility and safety profile of SARMs, given that changes in HDL levels are the most significant adverse effect of SARMs observed to date.

Alzheimer's disease

Androgen depletion is implicated in the development of Alzheimer's disease, as circulating testosterone levels in older men are inversely correlated with levels of amyloid β (Ab) protein in the brain (15). Hypogonadal men also experience a decrease in cognitive processes including episodic memory, working memory, processing speed, visual-spatial processing, and executive function (49,50), while a higher free testosterone index is associated with improved visual and verbal memory, visuospatial functioning, visual-motor scanning, and a lower rate of decline in visual memory (51). Given that these functions are regulated by AR-modulated regions of the brain (52), the potential impact of SARMs as a treatment for cognitive disorders associated with hypogonadism is significant. In 2013, the NEP28 SARM was found to increase the activity of an Aβ-degrading enzyme, neprilysin, without severe effects on the prostate (15). However, no further studies have investigated this compound.

Breast cancer

Improved breast cancer outcomes have been associated with increased androgen synthesis (53). However, androgens can also cause virilization in women. Being analogous to SERMs, which have differential effects on breast, bone, and uterine tissues (31), SARMs also exert their effects on breast tissue that expresses AR. Fortunately, improved breast cancer survival is correlated with AR expression (54), which occurs in up to 85% of ER-positive breast cancers and 95% of ER-negative breast cancers (55). This presents a unique opportunity for modulation by SARMs. In a press release from GTx Inc. regarding a recently completed phase II clinical trial (NCT02463032), Enobosarm slowed breast cancer growth in a subset of patients (20). Another ongoing phase II trial seeks to assess the treatment of AR-positive metastatic triple-negative breast cancer using cotherapy of pembrolizumab and Enobosarm (NCT02971761). Other
recently completed clinical trials examining SARM efficacy include: NCT02746328, which assessed the impact of 12–24 weeks of GTx-024 (Enobosarm) on neuromuscular function and lean body mass (LBM) in females with ER+/AR+ breast cancer, and NCT03264651, a completed phase I study which studied the impact of a combination treatment of 9 mg oral Enobosarm and 1 mg oral anastrozole on reducing breast density.

**Stress urinary incontinence (SUI)**

The efficacy of SARMs on levator ani muscle weight has been used as a surrogate for anabolic activity in skeletal muscle (38). However, the levator ani is also a key muscle in the pathophysiology of SUI. As women age, circulating hormones are depleted postmenopaually and pelvic floor muscles atrophy. Lacking support of the pelvic organs and the lower urinary tract, difficulty with micturition results.
Due to virilization and uterine hyperplasia, androgens are not an optimal treatment option for SUI, and presently no other medical therapies exist. Two SARMs, GTx-024 (Enobosarm) and GTx-027 (GTx-024 analog), have demonstrated preclinical potential for the treatment of SUI by selectively increasing pelvic floor mass in an ovariectomized mouse model (21). Reversal of muscle loss in post-menopausal mice was accompanied by a substantial downregulation of genes linked to muscle catabolism. This study presented a step toward the clinical evaluation of SARMs for the treatment of SUI, a problem that affects up to 35% of adult women (56).

Following a promising proof of concept study, a phase II clinical trial (NCT03241342; ASTRID) of GTx-024 was initiated. Post-menopausal women were placed on either placebo, 1 mg, or 3 mg oral GTx-024 therapy, and change in stress continence episodes from baseline was examined (57). Unfortunately, the study failed to meet its primary endpoint of achieving a 50% reduction in SUI daily episodes compared to the placebo. Two subsequent phase II studies (NCT03566290, NCT03508648) were terminated the same month, per http://www.clinicaltrials.gov. As such, the role of SARMs in the treatment of SUI is currently undefined.

Pca

Controversy still exists regarding whether TTh may stimulate latent PCa, limiting the application of TTh in the treatment of hypogonadism in men with a history of PCa (4,17). Solomon et al. recently reviewed two SARMs, FL442 and MK-4541, which have been tested/explored as treatments for PCa. FL442 acted as an AR antagonist in the PCa cell models with efficacy comparable to that of enzalutamide (4,58). Meanwhile, MK-4541 induced apoptosis in androgen-independent, AR-positive PCa cell lines (59).

The S42 SARM has emerged as a prospective treatment for PCa. Upon its initial discovery, S42 was observed to have anabolic effects on muscle while sparing the prostate (60). Only years later was its potential for PCa treatment considered in its suppression of PCa cell proliferation signaling components, including the 5-DHT-induced extracellular signal-regulated kinase (ERK)–mitogen-activated protein kinase (MAPK) pathway (17,61). In addition, S42 inhibited tumor growth by limiting the expression of prostate-specific antigen (PSA), P504S, Ki67, and phosphorylated ERK-MAPK (17). S42 also attenuated proliferation-related receptors, including insulin-like growth factor-1 receptor (IGF-1R), insulin receptor, and the AR. While S42 reduced tumor growth and antagonized DNA replication in PCa cells, it did not induce apoptosis (17).

One phase II clinical trial (NCT02499497) is investigating the efficacy of the SARM LY2452473 in improving symptom management in men with PCa, including sexual function, quality of life, and muscle and bone mass.

SARMs may also be used in the setting of PCa management for the targeted imaging of prostate tissue (62). Given the expression of the AR in every stage of PCa evolution, radioactively-labeled SARMs could be used for the radiological diagnosis of metastatic disease (63). These findings suggest another future benefit of SARMs in the evaluation and treatment of PCa.

BPH

One can envision the potential utility of SARMs as a treatment for BPH by acting as an AR antagonist. Zilbermint et al. observed that because SARMs are not metabolized to DHT by 5α-reductase, the risk of prostatic hyperplasia is reduced (30). While previous studies have observed that SARMs can decrease prostatic weight in rat models (18,43), a single phase II clinical trial (NCT03297398) was recently initiated to study the efficacy and safety of OPK-88004 in men with BPH. In the trial, patients were treated with either a placebo, 15, or 25 mg of OPK-88004 for 16 weeks. Monthly visits evaluated drug safety and plasma levels, as well as its effect on prostate size and lower urinary tract symptoms (LUTS). Unfortunately, this trial has since been terminated, and a press release disclosed that while serum PSA analysis has yet to be completed, the utilization of transrectal ultrasound for measuring prostate volume proved to be too imprecise to reliably determine the effect of the drug (64). In addition, transient increases in liver enzymes were observed in several men in the trial.

Male contraception

The prospect of SARMs as a method of male contraception has been yet another focus of investigation, especially given their apparent lack of significant side effects. Animal studies of two SARMs, C-6 and S-23, were examined by Solomon et al. in a recent review (4). In mouse models, S-23 demonstrated the potential to reversibly suppress spermatogenesis while also increasing lean muscle mass, bone mineral density, and decreasing fat mass (65). While...
SARM development appears to be focused on other areas of intervention, these preliminary findings are promising.

**Hypogonadism and sexual medicine**

SARMs may represent a promising potential alternative to TTh, which has been the mainstay of the treatment of hypogonadism. While the sexual benefits of TTh are well established, unlike exogenous testosterone, SARMs are orally active, nonaromatizable, non-virilizing, and tissue-selective, with a better side effect profile than TTh (66).

Previous studies have demonstrated the potential benefit of SARMs for libido in both female and male rats (67,68). In one study, treatment of male rats with the SARM LGD2226 resulted in an increased number of mounts, intromissions, and ejaculations compared with a control group (68). These results did not differ significantly from a group treated with the synthetic androgen, fluoxymesterone, suggesting that SARMs may represent a viable alternative to TTh in promoting male libido (4).

As elaborated upon in other sections of this review, many SARMs have shown the potential to treat male hypogonadal symptoms such as deficits in muscle mass and bone mineral density (10,69). Among others, the SARMs enobosarm and LY305 have shown the capacity to reverse the hypogonadal-related decline of muscle mass and bone density. LY305 did so while simultaneously avoiding adverse effects demonstrated by other SARMs such as decreased HDL and increased hematocrit. However, approval for SARMs in the treatment of male hypogonadism likely hinges upon “defining what constitutes a clinical deficit in these hypogonadal symptoms, and...defining what qualifies as a clinical benefit in ameliorating them” (31).

**Duchenne muscular dystrophy (DMD)**

DMD is a crippling genetic disorder that causes progressive muscle wasting and weakness because of mutations in the cytoskeletal protein dystrophin. Corticosteroids are currently the standard of care, but one side effect of their prolonged use is muscle wasting. The anabolic benefits of SARMs to muscle and bone without off-target androgenic side effects provides a distinct advantage to androgens. Previous work found that GLP0492 can increase body weight, muscle mass, diaphragm contractile force, and running performance in mice (4,23). In addition, as noted previously, LY305 reversed skeletal muscle atrophy by utilizing transdermal delivery, thus avoiding a rise in HDL.

In a comprehensive study, Ponnumamy et al. hypothesized that the absence of anabolic androgen activity exacerbated the rapidly diminishing health of young boys with DMD and that SARM treatment could reverse the decline in physical function and prolong life (24). When GTx-026, an analog of GTx-024, was used in castrated and dystrophin mutant mice, a decrease in fibrosis and increases in cardiopulmonary function, body weight, lean mass, grip strength, and survival were observed (24). GTx-026 was found to exert its effects through a pathway distinct from dystrophin-regulated pathways (24). In addition, SARM treatment had the potential to improve muscle regeneration, as measured by a reduction in centrally nucleated muscle cells (24).

**Muscle wasting**

The use of SARMs as a potential alternative to TTh for cancer-related cachexia or age-related sarcopenia has been desirable since their discovery (2,28,70). Due to their selective anabolic activity without associated androgenic side effects, SARMs may treat muscle wasting associated with many chronic conditions including heart failure, chronic obstructive pulmonary disease (COPD), HIV, end-stage liver and kidney disease, chronic infection, immobilization, and chronic glucocorticoid use (4,69,71). Studies have demonstrated that survival of cancer patients correlates directly with muscle mass (72-74) and that sarcopenia is associated with increased mortality (75). As such, testosterone is approved for the treatment of these conditions. However, recent clinical trials have suggested that the cardiac risks of TTh outweigh its therapeutic benefits (76,77). Although this controversy has not been resolved, SARMs are being considered instead of TTh to address the problem of muscle wasting. While early preclinical models showed SARMs to be effective in ameliorating muscle wasting by increasing lean body mass, recent clinical studies have cast doubt on their outlook.

Several phase I studies have recently evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of the SARM GSK2881078. In a study by Clark et al. (NCT02045940), a dose range of oral GSK2881078 was administered to healthy men and postmenopausal women for either 7 or 14 days and was associated with decreases in HDL, similar to what has been observed with other SARMs (4,19,78). Adverse events were noted in half of the study population, though these were distributed evenly between the placebo and active treatment groups, indicating that
the dose range was well tolerated (78). These early trials demonstrate a potential role for GSK2881078 in cachexia therapy.

In another phase I clinical investigation of GSK2881078, gains in lean mass were evaluated at various doses (29). While both male and female patients on all doses of GSK2881078 experienced greater lean mass gains than those on placebo, lower doses resulted in greater lean mass responses in females than in males (29). These dose-dependent gains were produced in the absence of any resistance training. Transient elevations in alanine aminotransferase (ALT) were observed but resolved despite continuing the drug, and reversible reductions in testosterone levels were observed in all men. Finally, a phase II trial (NCT03359473) evaluating the efficacy and safety of GSK2881078 in COPD is currently underway. In addition to safety, this trial is evaluating the effects of GSK2881078 on physical strength and function in both postmenopausal female and older male subjects with COPD and muscle weakness. These subjects will participate in a baseline period for 30 days, after which they will follow a home exercise program and treatment for 13 weeks, followed by a 6-week follow-up period during which subjects’ performance in various trials will be evaluated, such as leg press strength and vital.

A recent study by Muta et al. examined the impact of a novel SARM, S42, on the muscle cell line C2C12 in vitro, which was observed to have anabolic and anti-catabolic effects on myotubes of differentiating muscle cells (22). The anti-catabolic effects consisted of inhibition of the degradation pathway in C2C12 myotubes and decreased expression of skeletal muscle ubiquitin ligase. The anabolic effects of S42 included activation of the mTORC1–p70S6K signaling pathway, independent of IGF-1-Akt signaling. S42 may selectively encourage muscle growth while simultaneously minimizing certain undesirable effects such as prostate growth (22). These in vitro results hint at the ability of SARMs to both prevent muscle loss and induce muscle gains in patients who suffer from muscle wasting conditions.

Unfortunately, results of recent clinical trials of the SARM GTx-024 (Enobosarm) have tempered expectations for its utility as a therapy for muscle wasting. Early on, GTx-024 appeared to have a very bright future as a treatment for sarcopenia/cachexia. Preliminary clinical trials demonstrated that GTx-024 could increase lean body mass and improve physical function without androgenic side effects (27). However, Enobosarm was dealt a blow after the phase III Prevention and treatment Of muscle Wasting in patients with cancER (POWER) I and II trials, where increases in lean body mass were once again observed, but without improved stair climb power (79,80). Failure to attain both primary endpoints led to a lack of approval by the Food and Drug Administration (FDA), which has cast doubt on the previously charted course for SARMs and has tempered enthusiasm regarding the role of SARMs in the treatment of muscle wasting conditions.

Cachexia controversy

In 2015, Bhasin noted that “functional exercise training may be necessary to translate the physiological benefits of SARMs into functional improvements” (39). Indeed, following the recent challenges for SARMs and cachexia, a similar concern was shared by Ramage & Skipworth, who noted that “The relationship between muscle mass and muscle function is complex and unlikely to be linear” (80). Again, Dalton et al. lamented that “proving that SARM-induced increases in lean body mass (i.e., muscle) are associated with improvements in physical function appears to the greatest barrier to their regulatory approval and clinical use” (31).

While the results of the phase III POWER trials demonstrated that Enobosarm (Gtx-024) could induce measurable and meaningful gains in lean body mass, there was no significant accompanying improvement in physical function (31). Presumably, this is due to confounding factors including age, disease stage, baseline physical function, and chemotherapy, but the fact remains that a definitive correlation between lean body mass and physical function in a large patient population has “remained elusive for a SARM” (31). This barrier, however, extends beyond just SARMs. At this time, no drug has been approved by the FDA to treat cancer cachexia (71). Indeed, in the ROMANA anamorelin trials, significant increases in LBM were not accompanied by gains in handgrip strength (81). Therefore, in trials of both Enobosarm and anamorelin, despite measurable gains in LBM, lack of correlated improvements in physical function resulted in a negative regulatory interpretation of the trials and lack of FDA approval (71). Merely preventing a decline in performance was also not considered to be an acceptable outcome (82).

One of the most significant obstacles for approval of SARMs as a future treatment for cachexia is both a lack of consensus on proper endpoints for clinical trials and a drought of regulatory direction (71,82). Unfortunately, these shortfalls have led to the standstill of many promising
drugs in spite of a significant unmet medical need (71). Given that cachexia is defined by the presence of three essential elements: muscle loss and change in body composition, impaired nutrition, and decline in physical function (83), it has been suggested that treatment best be evaluated simply by patient responses to these domains. It should be noted that, despite the logic that proper nutrition be accompanied by exercise to achieve functional gains, one systematic review found “insufficient evidence in the safety and effectiveness of exercise in cancer cachexia patients” (84). Therefore, the requirement that a SARM must improve physical function in order to gain approval may be unreasonable. As such, to push forward with well-designed clinical trials that further define the efficacy of SARMs in cachexia and sarcopenia, appropriate clinical trial endpoints must be developed.

Potential for abuse

Performance-enhancing drugs, such as exogenous testosterone, have long been a concern in professional athletics and have resulted in anti-doping measures. SARMs, with their attractive side effect profile, ease of use, and relative difficulty to detect compared to other androgenic compounds, present a significant potential for abuse (85,86). Indeed, despite not being approved by the FDA, SARMs are readily available for purchase online (4). However, though marketed as SARMs, one study found that many of these online offerings are inaccurately labeled and contain unapproved substances, with only 52% containing the active SARM (87). Conversely, ostarine has been found as both a listed and unlisted ingredient in many dietary supplements (88).

As such, efforts are currently focused on continuing to isolate metabolites from novel SARMs for drug testing (89,90), and multiple SARMs have already been added by the World Anti-Doping Agency (WADA) to the Prohibited List (91). Consequently, several athletes have been suspended for testing positive for SARM metabolites; an NBA athlete was recently suspended for taking LGD-4033 (92), while an NCAA basketball player and four UFC fighters have been penalized for trace amounts of ostarine (Enobosarm) in their systems (88,93). As novel SARMs are discovered and become available, regulating their use may become a challenge. Furthermore, once FDA approval occurs, significant potential for off-label use is likely, depending on the drug and its effects.

Conclusions

Widely expressed throughout the human body, the AR plays a role in sexual development and many other processes such as growth and maintenance of muscle and bone. Tissue-dependent patterns of AR expression, along with varied transcriptional coregulation, allow for diversity of actions when the AR is combined with its ligand. SARMs are chemically engineered drugs that can selectively exert varying degrees of agonist and antagonist effects on the AR, depending on their structure. This allows for targeted therapeutic benefits with the absence of adverse off-target effects, which is currently a significant limitation of TTh. SARMs are well tolerated, and their oral bioavailability provides a substantial advantage over other methods of androgen therapy. Finally, the potential for transdermal administration may circumvent hepatic metabolism and negate decreases in HDL, one of the only significant side effects of SARMs observed to date.

SARMs have demonstrated the ability to preferentially stimulate bone and muscle growth, shrink the prostate, and inhibit breast cancer growth. This variety of tissue selectivity may enable SARMs to treat a wide range of diseases, from muscle wasting and osteoporosis to hypogonadism and BPH. However, while SARMs have shown potential to ameliorate numerous serious and therapy-deficient pathologies, much remains to be examined regarding their efficacy, and regulatory approval remains elusive. The future use of SARMs for treatment of cachexia is currently tentative because of a lack of consensus regarding endpoints for clinical trials. As such, the future of SARMs may hinge on their use for other indications such as PCa, breast cancer, and osteoporosis. Nevertheless, there is still considerable confidence that SARMs have the potential to provide revolutionary treatment for diverse medical challenges.

Acknowledgments

Funding: AW Pastuszak is a National Institutes of Health (NIH) K08 Scholar supported by a Mentored Career Development Award (K08DK115835-01) from the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported in part through a Urology Care Foundation Rising Stars in Urology Award (to AW Pastuszak). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Footnote

Conflicts of Interest: AW Pastuszak: Endo Pharmaceuticals – advisor, consultant, speaker, research support; Boston Scientific – advisor; Antares Pharmaceuticals – advisor; Bayer AG- speaker. JM Hotaling: Endo pharmaceuticals – research support, educational grant; Boston Scientific – educational grant; StreamDx, Inherent Biosciences, Andro360, Nanonc – equity/founder of early stage startups; Turtle Health – advisor. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

20. GTx Reports Results from Ongoing Enobosarm Phase 2 Clinical Trial in ER+/AR+ Breast Cancer., Biospace.


90. Piper T, Dib J, Putz M, et al. Studies on the in vivo...


93. What you need to know about Ostarine, the drug found in Wildcats star Allonzo Trier’s system. Arizona Daily Star. 2018 February 23, 2018.