IS SARM - Selective Androgen Receptor Modulator: A Chance for Therapeutic Approach in Muscle-Wasting Chronic Conditions?

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DOI:
10.32098/mltj.02.2024.17

LEVEL OF EVIDENCE: 5

INTRODUCTION
Androgens (testosterone and dihydrotestosterone (DHT)) are the male sex hormones required for development of the male reproductive system and secondary sexual characteristics (1). Androgens actions are mediated via the androgen receptor (AR), modulating functions as a transcription factor (2) (figure 1). AR is a ligand-dependent nuclear transcription factor and member of the steroid hormone nuclear receptor family. AR is expressed in multiple reproductive tissues, with important effects on multiple organ

SUMMARY
Purpose of review. The purpose of this paper is to review the current concepts regarding a new-old pharmacological class, SARM (Selective Androgen Receptor Modulator). Especially how SARM can be beneficial in treatment of orthopedic disease.

Materials and methods. Androgens (testosterone and dihydrotestosterone (DHT)) are the male sex hormones required for development of the male reproductive system and secondary sexual characteristics. SARMs due to ability to bind androgen receptor are excellent in treatment of various diseases.

Discussion. Based on the published literature, a review has been carried out on SARM and its fields of application in the treatment of muscle wasting pathologies. Starting from the history of the SARMs, its role in prevention of muscle wasting, anabolic effects and side effects were addressed.

Conclusions. Nonsteroidal SARMs are unique in their ability to bind the androgen receptor with high affinity and exhibit tissue selective activity. SARMs can be used to treat muscle wasting conditions, osteoporosis, frailty syndrome without unwanted side effects associated with androgens.

KEY WORDS
SARM; SERM; muscle-wasting; cachexia; sarcopenia.
systems (3, 4). These play critical roles in the regulation of many male, and female sexual, somatic and behavioral functions critical to lifelong health, like bone density, strength muscle mass, coagulations, cognition, metabolism (5, 6) (table I).

Low endogenous testosterone concentrations are associated with sarcopenia and frailty due to decreased muscle mass, and bone mineral density. Testosterone replacement therapy is potential benefit, but is often curtailed of side effects like erythrocytosis, hepatotoxicity, testicular atrophy, prostate hypertrophy, aromatization to estrogen (7, 8). To avoid these side effects, molecules capable of selectively binding and modulating the androgen receptor have been developed since the 2000s (9). This is how SARMs (Selective Androgen Receptor Modulator) were born, to bypass the pharmacological and pharmacokinetic limitations of steroid (10). SARMs have been chemically engineered to target AR function more specifically in certain tissues because of tissue specificity and not being substrates for aromatase or 5-α reductase (4).

MATERIALS AND METHODS

Search strategy

The literature search of the present narrative review was conducted according to this protocol:

- SARM.
- Linkage about SARM and muscle wasting.
- AR, SARM, muscle wasting, cachexia, sarcopenia.

Literature search

In March 2023 the following databases were accessed: PubMed, Embase, Scopus, Web of Science, Google Scholar. The following keywords were used in combination: AR, SARM, muscle wasting, cachexia, sarcopenia. If title and abstract matched the topic, the full text was accessed. The bibliographies of the full-text articles were also screened for inclusion. Disagreements were solved by a third author. All the articles that investigate possible use of SARMs for muscle wasting pathologies. According to the authors language capabilities, articles in English, French, German, Italian, and Spanish were considered.
DISCUSSION

Based on the published literature, a review has been carried out on SARM and its fields of application in the treatment of muscle wasting pathologies. Starting from the history of the SARMs, its role in prevention of muscle wasting, anabolic effects and side effects were addressed.

History of Selective Androgen Receptor Modulator (SARM)

The history of SARMs begins in 1990 with the development of a drug, tamoxifen, a so-called SERM (selective estrogen receptor modulator), used in the treatment of breast cancer, which stimulated interest in analogous drugs to modulate the androgen receptor (AR) (11, 12). As demonstrated by the development and clinical use of SERMs like tamoxifen, the key characteristic underlying the therapeutic potential of SARMs is their tissue specificity. Several labs began working on identifying lead candidates and specific pharmacophores from 2000 to today, with from 2000 to now, with the design of 4 categories of SARMs pharmacophores (table II). The first preclinical evidence for tissue-selective activation of the AR was that arylpropionamide SARMs increased levator ani muscle weight in castrated rats to the level of sham-operated rats, but only partially increased the prostate and seminal vesicles weight (16, 17). Over the next decade structure-activity relationship studies were conducted on the arylpropionamide class of SARMs that culminated in two clinical candidates, with enobosarm being the most advanced in clinical development (17, 18). In addition to their effects on muscle, enobosarm and other arylpropionamide SARMs also demonstrated beneficial effects on bone (19). Enobosarm has been evaluated in several phase II and phase III clinical trials for multiple indications (5, 6, 20).

Ligand Pharmaceuticals developed tricyclic quinolinones that coincided with the discovery of arylpropionamide SARMs (21, 22). Similar to the arylpropionamide SARMs, these quinolinones also bind to and activate the AR in low nanomolar concentrations while eliciting tissue-selective activation of the AR in muscle.

Based on structure activity relationship of several SARM templates, Ligand Pharmaceuticals synthesized LGD2226 as their first clinical candidate (23). LGD2226 demonstrated myo- and osteo-anabolic activity and maintenance of sexual function in various preclinical models.

Muscle wasting chronic conditions

Weight loss can be considered as a warning sign in the progression of various diseases, acute or chronic. “Muscle wasting disease” (MWD) means an integrative association of age-related sarcopenia and chronic disease-related cachexia (24), this condition is observed in a variety of pathologies such as cancer, chronic kidney disease as well as after prolonged inactivity or during aging (table III). Cachexia is a multi-organ syndrome associated with cancer and other chronic diseases, characterized by body weight loss, muscle and adipose tissue wasting and inflammation, being often associated with anorexia (25, 26). Sarcopenia is characterized by a progressive loss of muscle mass, function, and physical performance during aging (27). The incidence of sarcopenia reaches up to 5-13% in 60-70 years old population and 11-50% in those at 80 years or above (28). Muscle wasting is the result of a combination of an imbalance between synthetic and degradative protein pathways together with increased myocyte apoptosis and decreased regenerative capacity (29).

<table>
<thead>
<tr>
<th>Table II. SARMs pharmacophores.</th>
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<tbody>
<tr>
<td>Categories</td>
</tr>
<tr>
<td>Aryl-Propionamide</td>
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<tr>
<td>Bycyclic Hydantoin</td>
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<tr>
<td>Quinoline</td>
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<tr>
<td>Tetrahydroquinoline</td>
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</table>

| Table III. Pathways of Modalities for Muscle Wasting Disease (MWD). |
|---------------------------------|---------------------------------|
| Cachexia | Sarcopenia |
| High Inflammation | Chronic Inflammation |
| Reduction in muscle mass and strength | Reduction in muscle contractibility |
| Mitochondrial Disfunction | Alterations in protein turnover |
| Anabolic Resistance | Apoptosis |
| Insulin resistance | Impaired regeneration |
Loss of muscle mass is associated with higher morbidity and mortality which translate in reduced quality of life (30). Over the years many efforts have been made to treat these conditions while avoiding further adverse effects on the already precarious health of these people. Physical activity and diet, through changes in microbiota are the main activities for the management of these conditions (31). However, it is understood that in some cases it is difficult to implement these principles (32). Currently no products approved for treatment of muscle wasting secondary to age or chronic disease states, including cancer. Most of the current treatment options have focused on stimulating nutritional intake or reversing some of the inflammatory processes involved in cachexia.

Most studied SARMS are Ostarine, Andarine, Enobosarm developed by GTx and Merck & Co. Inc. which arrived in Enobosarm case also in Phase III of pharmaceutical development (38). Enobosarm might offer a promising option for the prevention and treatment of muscle wasting due to cancer by increasing muscle mass without the side effects associated with non-selective anabolic androgenic steroids or with growth hormone or growth hormone-releasing hormone therapies. Enobosarm resulted also in larger improvements in lean body mass and physical function in healthy older men and postmenopausal women (20, 38). Ostarine although is a non-steroidal SARM, tested in Phase I and II clinical trials, demonstrating a safety profile, an high tissue selectivity with beneficial effects on lean body mass and improving physical performance.

**CONCLUSIONS**

Nonsteroidal SARMS are unique in their ability to bind the androgen receptor with high affinity and exhibit tissue selective activity. SARMS can be used to treat muscle wasting conditions, osteoporosis, frailty syndrome without unwanted side effects associated with androgens. Last clinical trials for SARMS were in 2013, so 10 years have gone and appear to be no studies to explore the extraordinary capabilities of these drugs. SARMS are not FDA (Food and Drug Administration) approved, but recently they are being used by gym goers, with an high risk for health, because of fake product. A return in clinical trials is required to assess the role of nonsteroidal SARMS and if they can be used in near future.

**FUNDINGS**

None.

**DATA AVAILABILITY**

Data are available in the review.

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**Table IV. Therapeutic Modalities for MWD.**

<table>
<thead>
<tr>
<th>Modalities</th>
<th>Function</th>
<th>Limitation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Appetite Stimulants (Corticosteroids and Megestrol acetate)</td>
<td>-Increase food intake and produce weight gain</td>
<td>-Limited long-term benefits on quality life</td>
<td>Behl <em>et al.</em> (33)</td>
</tr>
<tr>
<td>Thalidomide, Cox-2 inhibitor COLECOXIB, anti IL-6</td>
<td>-Targets the inflammation associated with MWD</td>
<td>-Chest pain</td>
<td>Tazi <em>et al.</em> (34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Confusion</td>
<td>Mantovani, <em>et al.</em> (35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Shortness of breath or difficulty breathing</td>
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<td></td>
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<td>-Swelling</td>
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<td></td>
<td></td>
<td>-Nausea</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>-Act on GH receptors to increase appetite,</td>
<td>-Short half-life</td>
<td>Garcia <em>et al.</em> (36)</td>
</tr>
<tr>
<td></td>
<td>-GH secretion and lean body mass</td>
<td>-Administration via inj.</td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td>-Anabolic qualities</td>
<td>-Cardiovascular events</td>
<td>Giovanelli <em>et al.</em> (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Hepatotoxicity</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>-Increase hematocrit</td>
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CONTRIBUTIONS
AB, SZ: literature search, data extraction, risk of bias assessment, writing - original draft, writing - review & editing.
GO: risk of bias assessment, writing - original draft, writing - review & editing.
NM: writing - original draft, writing - review & editing.
FC: conceptualization, design, risk of bias assessment, writing - original draft, writing - review & editing.

REFERENCES

CONFLICT OF INTERESTS
The authors declare that they have no conflict of interests.