https://doi.org/10.31925/farmacia.2018.5.3 **REVIEW**

SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMs) IN THE CONTEXT OF DOPING

AMALIA MIKLOS *, AMELIA TERO-VESCAN, CAMIL-EUGEN VARI, BIANCA-EUGENIA ŐSZ, CRISTINA FILIP, CARMEN-MARIA RUSZ, DANIELA-LUCIA MUNTEAN

University of Medicine, Pharmacy, Sciences and Technology, Faculty of Pharmacy, 39 Gheorghe Marinescu Street, 540139, Târgu Mureş, Romania

**corresponding author: amalia.miklos@umftgm.ro*

Manuscript received: February 2018

Abstract

Selective androgen receptor modulators (SARMs) are substances of increasingly interest in the medical area due to the anabolic effect on muscle and bone tissue. Even if they aren`t yet introduced into therapy, they are in various stages of experimental and clinical research for pathologies involving catabolic states in protein metabolism. These molecules manage to dissociate the anabolic effect from the virilising effect, compared with androgenic hormones, due to the non-steroidal structure that they detain. Having this pharmacological advantage, besides the possibility of being orally administered, these substances are used illegally by athletes and bodybuilders. It is important to note that SARMs are prohibited for performance athletes by World Anti-Doping Agency (WADA), but the concern is that they can be easily obtained from various uncertain sources. Moreover, their pharmacotoxicological profile is not clearly known, so their chronic administration, in high doses, represents a possible risk for the health.

Rezumat

Modulatorii selectivi ai receptorilor androgenici (SARM) sunt substanțe de interes crescut în aria medicală datorită efectelor anabolice la nivelul țesutului muscular și osos. Chiar dacă nu sunt introduse încă în terapie, sunt incluse în diverse stadii de cercetare experimentală și clinică pentru tratarea patologiilor cu stări catabolice în metabolismul proteic. Aceste molecule reușesc să disocieze efectul anabolic de cel virilizant, în comparație cu hormonii androgeni, datorită structurii lor nesteroidice. Deținând acest avantaj farmacologic, pe lângă posibilitatea de a fi administrate oral, aceste substanțe se utilizează în scop ilicit de către atleți și culturiști. Este important de menționat faptul că aceste substanțe sunt interzise sportivilor de performanță de către *World-Anti Doping Agency* (WADA), dar totuși pot fi ușor de procurat din diverse surse nesigure. În plus, profilul lor farmaco-toxicologic nu este suficient cunoscut, deci administrarea cronică, în doze mari, reprezintă un posibil risc pentru sănătate.

Keywords: SARM, doping, risk

Introduction

Selective androgen receptor modulators (SARMs) are substances with anabolic activity and of great interest over the last two decades in the medical area, being considered a possible therapeutic pathway for pathologies involving bone damage, weakness or muscle atrophy [5, 35, 37].

As their name suggests, SARM molecules act selectively as agonists on the androgen receptors located in the muscle and bone tissue, without influencing the receptors located in androgen dependent tissues (testis, prostate, skin). Although they are considered to have an important therapeutic potential in muscle or bone disorders, the concern is that there is no clear evidence of their safety in chronic administration and the adverse effects produced are not certainly known. These substances have been discovered since 1998, and despite the passage of time, they have no marketing approval and cannot be used in therapy, although there are a variety of studies that sustain their usefulness in cachexia, sarcopenia, osteoporosis or hypogonadism and even in a certain type of breast cancer, inhibiting the development of tumours and stopping metastasis [7, 22, 26, 27, 28].

In terms of structure characteristics, these molecules are divided into four categories: bicyclic hydantoins, quinolines, tetrahydroquinolines and arylpropionamide analogues. The arylpropionamides category was discovered using bicalutamide as structural model. It is also supposed that the initiative of developing these molecules derived from the SERM concept (selective estrogen receptor modulators) [42].

The great advantage of SARMs concept in medical area is to substitute testosterone replacement therapy in certain pathologies like hypogonadism, due to the lack of steroid-related side effects in long-term administration, with high oral bioavailability, good absorption rate, being considered a wonderful steroid alternative [20, 29].

There are a number of studies provided by the scientific literature describing research on phase I, II or even

phase III clinical trials performed to sustain the efficacy of SARMs in the treatment of sarcopenia, muscle wasting in cancer patients and even studies regarding the pharmacokinetic drug interactions between SARMs and other drugs [3, 6, 30, 8]. In addition to studies describing the therapeutic efficacy, scientific literature outlines the doping control methods [40]. Due to the advantages regarding the specificity and selectivity of action only on bone and muscle tissue, these substances are used as doping agents by athletes, bodybuilders, and also among adolescents, being categorized as "body image enhancing drugs".

The aim of this mini-review is to highlight that the discovery of SARMs is beneficial for the future development of novel therapies with minimal side effects, in pathologies with bone or muscle impairment, but the abuse of certain SARMs sold on the black market or *via* the internet represent a real risk for the health because their long-term effects aren`t sufficiently studied. Moreover, these substances available as food supplements may contain other components besides the molecule of interest, not being controlled and tested properly.

SARM-mechanism of action

The androgen receptors (AR) are classified as nuclear receptors, having as physiological ligands the hormone testosterone and its active form, dihydrotestosterone. The localization of AR receptors is various on human body, but they are predominant in testis, prostate, skin, muscles, bones, brain. It is important to mention that testosterone acts to the AR receptors located in muscles and bones, but the AR receptors located in skin, testis, prostate have as physiological agonist, dihydrotestosterone (biosynthesized from testosterone under the action of the enzyme 5α-reductase) [33]. SARMs act as agonists to the AR receptors located in bones and muscles, being antagonists (in the presence of dihydrotestosterone) to the AR located at the level of androgen dependent tissues (testis, prostate, skin etc) [16, 47].

There are recent studies focusing on the improvement of binding the SARM molecule to the AR, taking into account changes in the structure of the molecule so as to increase its lipophilicity to cross more easily the cell membrane and to improve the efficacy of the substance [2, 4, 15, 24]. A similar optimization was applied when discovering ostarine molecule, starting from the structural model of andarine. The difference between andarine (S-4) and ostarine (enobosarm), besides the molecular structure, is the half-life. Andarine has a half-life of 4 hours, compared to 24 hours half-life for ostarine. Moreover, ostarine has stronger anabolic effects, may be administered in smaller doses and once daily, compared to andarine [9, 14, 19]. Regarding ostarine, named also as GTx-024 or enobosarm, Ponnusamy S. *et al*. demonstrated a beneficial effect on the growth of pelvic floor muscle mass in post-menopausal ovariectomized mice, as such, these molecule could become effective in stress urinary incontinence [32].

SARMs real advantages lie in the fact that they do not have a steroidal structure like androgen hormones, not being substrates for type 2 5α-reductase [25]. The enzyme 5α-reductase is present mostly in male sexual organs, hair follicles, but not in anabolic tissues such as bone and muscle, which explains SARM tissue selectivity, managing to dissociate the anabolic action from the androgenic action.

On the other hand, these structures are not substrates for aromatase and are not transformed into oestrogens, so they do not affect the hypothalamus-pituitary axis. Physiologically, testosterone and oestradiol negatively regulate through negative-feedback the hypothalamic pituitary axis, with the decrease of circulating levels of testosterone [12, 23, 44, 45].

Differences between SARMs and testosterone derivatives

As it is known, the use of anabolic substances with the potential to enhance athletic performance is prohibited by the regulations of World Anti-Doping Agency (WADA). Regarding their anabolic effects on bone and muscle tissues, SARMs are used for doping purposes and are listed on the the Prohibited list of WADA since 2008, in the anabolic agents category (S1) [48, 49]. Although there are not studies regarding their safety in chronic administration, they can be bought freely from the internet or through the black market. There are studies in which these substances have been found in other non-controlled preparations sold on the black market or showed differences between the claimed composition and the real composition when tested in laboratory [43, 38].

The difference between doping with steroids, respectively with SARMs, is that the long-term side effects such as hypogonadism due to hypothalamic-pituitary axis suppression, gynecomastia, testicular atrophy, sexual dysfunction or alopecia usually occurring after administration of testosterone derivatives do not appear, due to the non-steroidal structure detained [34]. Other side effects produced by chronic administration of steroids are arrhythmia, dyslipidaemia, pathological remodelling in the heart, hypertension, thrombosis, erythrocytosis, neuro-psychiatric and behavioural disorders, effects that are not described after SARMs administration [11, 46].

Moreover, recent studies suggest the beneficial action of SARMs at the level of AR receptors located in the central nervous system. SARM RAD140 proved to have positive effects in neuronal cells, reducing the apoptosis process [17].

To make the differences clearer between SARMs and testosterone (T) derivatives characteristics, the

pharmacokinetic, pharmacodynamic and pharmaco-toxicological aspects are highlighted in the table below (Table I).

Table I

The differences between SARMs and testosterone derivatives regarding the pharmacokinetic, pharmacodynamic and pharmacotoxicological aspects

Testosterone derivatives	SARMs
Pharmacokinetic aspects	
The route of administration for the majority of the T derivatives is by injection (intra-muscular) and the plasmatic concentrations are fluctuant.	The route of administration is oral, having good bioavailability, increased absorption rate, prolonged effect, being administered once daily.
Pharmacodynamic aspects	
Their action is nonspecific, influencing all AR.	Acts specifically and selectively on the AR from muscle and bone tissue.
Pharmacotoxicological aspects	
Reproductive system disorders (e.g. hypogonadism, prostate hyperplasia)	Without damage or minimal effects on the reproductive system
Behavioural and aggressive disorders	Insufficient studies
Liver damage [11,18]	Insufficient studies
Dermatological side effects (acne)	Insufficient studies
Gynecomastia and feminising signs in men	Without feminizing signs
Cardiac system disorders	Insufficient studies
Alopecia	Without alopecia tendency

Regarding the pharmacological profile of SARMs highlighted in Table I, it can be concluded that these substances do not have a clearly defined pharmaco-toxicological profile, despite the pharmacokinetic and pharmacodynamic advantages and despite the years since they were discovered. This matter raises a question mark regarding their safety in chronic administration.

Analytical aspects in doping control

Currently, scientific literature offers a variety of studies on different LC-MS/MS (liquid chromatography tandem mass spectrometry) methods for identifying and quantifying these compounds in different biological matrixes (plasma, urine) for doping control, evidence that these substances are of widespread use and are of major interest in the athletic community [21, 36, 39].
Liquid chromatography coupled with mass spectrometry is an advanced method used in clinical laboratories due to the advantages of detecting molecules in extremely low concentrations (pg/mL), specificity, sensitivity, short analysis times, being considered a "gold standard" for the determination of hormones and doping agents from complex biological matrices [10]. Referring to andarine, also called acetamido-xolutamide, GTx007 or S-4, a case report was described in an in-competition female athlete urine sample, in which glucuronidates metabolites were detected, proving that the athlete used andarine for illicit purposes [13]. Since 2010, the number of doping cases has increased in time [1, 41].
Following the controversy in the literature, the conclusion would be that clinical trials that monitor the adverse effects of these compounds are difficult to achieve, primarily because they are not ethical due to the high doses used in doping. Another issue would be that some of the substances used are not registered as SARMs or can be found hidden in food supplements, so the only way to inform about this are reported cases or retrospective studies and research on experimental animals.
Although there are a variety of studies on LC-MS or GC-MS methods for detecting the doping with SARMs, it seems that they should still be optimized to avoid the false results due to the structural similarity of active metabolites of SARMs with androgen receptor antagonists such as flutamide [31].

Conclusions

SARMs are still intensively investigated regarding the development of new candidate molecules that could substitute testosterone replacement therapy in different pathologies, in order to avoid the related side-effects after chronic administration.
Being consumed for doping purposes due to their specific mechanism of action, more studies regarding their pharmacotoxicology should be conducted to investigate their risks after long-term administration.
Furthermore, the pharmaceutical forms available from different unsafe sources, do not have the certainty about the identity, quality, quantity of the molecule of interest.
Doping control methods (especially LC-MS methods) should still be optimized to identify and quantify, selectively and specifically, as low as possible concentration levels of SARMs in different biological matrices, in order to decrease the temptation to be consumed for illicit purposes.

References

1. Abushareeda W, Vonaparti A, Saad KA, Almansoori M, Meloug M, Saleh A, Aguilera R, Angelis Y, Horvatovich PL, Lommen A, Alsayrafi M, High resolution full scan liquid chromatography mass spectrometry comprehensive screening in sports antidoping urine analysis. *J Pharm Biomed Anal.*, 2018; 151: 10-24.
2. Aikawa K, Asano M, Ono K, Habuka N, Yano J, Wilson K, Fujita H, Kandori H, Hara T, Morimoto M, Santou T, Yamaoka M, Nakayama M, Hasuoka A, Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs) Part III: Discovery of 4-(5-oxopyrrolidine-1-yl) benzonitrile derivative 2f as a clinical candidate. *Bioorganic Med Chem Lett.*, 2017; 25: 3330-3349.
3. Aro HT, Kulkova J, Moritz N, Kähkönen E, Mattila RH, Local delivery of a selective androgen receptor modulator failed as an anabolic agent in a rat bone marrow ablation model. *Acta Orthop Scand.*, 2015; 86(6): 751-759.
4. Asano M, Hitaka T, Imada T, Yamada M, Morimoto M, Shinohara H, Hara T, Yamaoka M, Santou T, Nakayama M, Imai Y, Habuka N, Yano J, Wilson K, Fujita H, Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs). Part II: Optimization of 4-(pyrrolidin-1-yl) benzonitrile derivatives. *Bioorganic Med Chem Lett.*, 2017; 27: 1897-1901.
5. Clark RV, Walker AC, Andrews S, Turnbull P, Wald JA, Magee MH, Safety, pharmacokinetics and pharmacological effects of the selective androgen receptor modulator, GSK2881078, in healthy men and postmenopausal women. *Br J Clin Pharmacol.*, 2017; 83(10): 2179-2194.
6. Coss CC, Jones A, Dalton JT, Pharmacokinetic drug interactions of the selective androgen receptor modulator GTx-024 (Enobosarm) with itraconazole, rifampin, probenecid, celecoxib and rosuvastatin. *Invest New Drugs,* 2016; 34(4): 458-467.
7. Coss CC, Jones A, Hancock ML, Steiner MS, Dalton JT, Selective androgen receptor modulators for the treatment of late onset male hypogonadism. *Asian J Androl.*, 2014; 16: 256-261.
8. Crawford J, Prado CM, Johnston MA, Gralla RJ, Taylor RP, Hancock ML, Dalton JT, Study design and rationale for the Phase 3 clinical development program of Enobosarm, a selective androgen receptor modulator, for the prevention and treatment of muscle wasting in cancer patients. *Curr Oncol Rep.*, 2016; 18: 1-11.
9. Foster WR, Car BD, Shi H, Levesque PC, Obermeier MT, Gan J, Arezzo JC, Powlin SS, Dinchuk JE, Balog A, Salvati ME, Attar RM, Gottardis MM, Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *Prostate*, 2011; 71: 480-488.
10. Fülöp I, Vari CE, Miklos A, Imre S, LC-MS/MS ESI methods for the determination of oestrogens and androgens in biological matrix – a minireview. *Farmacia,* 2017; 65(4): 485-493.
11. Goldman A, Basaria S, Adverse health effects of androgen use. *Moll Cell Endocrinol.*, 2018; 15; 464: 46-55.
12. Ghosh D, Egbuta C, Lo J, Testosterone complex and non-steroidal ligands of human aromatase. *J Steroid Biochem Mol Biol.*, 2018; 181:11-19.
13. Grata E, Perrenoud L, Saugy M, Baume N, SARM-S4 and metabolites detection in sports drug testing: A case report. *Forensic Sci Int.*, 2011; 213: 104-108.
14. Haendler B, Cleve A, Recent developments in antiandrogens and selective androgen receptor modulators. *Moll Cell Endocrinol.*, 2012; 352: 79-91.
15. Handlon AL, Schaller LT, Leesnitzer LM, Merrihew RV, Poole C, Ulrich JC, Wilson JW, Cadilla R, Turnbull P, Optimizing ligand efficiency of Selective Androgen Receptor Modulators (SARMs). *ACS Med Chem Lett.*, 2015 19; 7(1): 83-88.
16. Hunter I, Hay CW, Esswein B, Watt K, McEwan IJ, Tissue control of androgen action: The ups and downs of androgen receptor expression. *Moll Cell Endocrinol.*, 2018; 465: 27-35.
17. Jayaraman A, Christensen A, Moser VA, Vest RS, Miller CP, Hattersley G, Pike CJ, Selective androgen receptor modulator RAD140 is neuroprotective in cultured neurons and kainate-lesioned male rats. *Endocrinol.*, 2014; 155: 1398-1406.
18. Kanayama G, Pope HG, History and epidemiology of anabolic androgens in athletes and non-athletes. *Moll Cell Endocrinol.*, 2018; 464: 4-13.
19. Kim J, Wang R, Karen AV, Dalton JT, Absorption, distribution, metabolism and excretion of the novel SARM GTx-024 [(S)-N-(4-cyano-3-(trifluoromethyl)-phenyl)-3-(4-cyanophenoxy)-2-hydroxy-2 methyl-propanamide] in rats. *Xenobiotica*, 2013; 43(11): 993-1009.
20. Krishnan V, Patel NJ, Mackrell JG, Sweetana SA, Bullock H, Ma YL, Waterhouse TH, Yaden BC, Henck J, Zeng QQ, Gavardinas K, Jadhav P, Saeed A, Garcia-Losada P, Robins DA, Development of a selective androgen receptor modulator for transdermal use in hypogonadal patients. *Andrology*, 2018; 6(3): 455-464.
21. Krug O, Thomas A, Walpurgis K, Piper T, Sigmund G, Schänzer W, Laussmann T, Thevis M, Identification of black market products and potential doping agents in Germany 2010–2013. *Eur J Clin Pharmacol.*, 2014; 70(11): 1303-1311.
22. Megumi M, Katsuji A, Takahito H, Masuo Y, Prevention of body weight loss and sarcopenia by a novel selective androgen receptor modulator in cancer cachexia models. *Oncol Lett.*, 2017; 14: 8066-8071.
23. Mohler ML, Bohl CE, Jones A, Coss CC, Narayanan R, He Y, Hwang DJ, Dalton JT, Nonsteroidal selective androgen receptor modulators (SARMs): Dissociating the anabolic and androgenic activities of the androgen receptor for therapeutic benefit. *J Med Chem.*, 2009; 52(12): 3597-3617.
24. Morimoto M, Amano Y, Oka M, Harada A, Fujita H, Hikichi Y, Tozawa R, Yamaoka M, Amelioration of sexual behavior and motor activity deficits in a castrated rodent model with a selective androgen receptor modulator SARM-2f. *Plos One*, 2017; 12(12): 1-14.

25. Motofei IG, Rowland DL, Baconi DL, Georgescu SR, Paunică S, Constantin VD, Bălălău D, Paunică I, Bălălău C, Baston C, Sinescu I, Therapeutic considerations related to finasteride administration in male androgenic alopecia and benign prostatic hyperplasia. *Farmacia*, 2017; 65(5): 660-666.
26. Narayanan R, Ahn S, Cheney MD, Yepuru M, Miller DD, Steiner MS, Dalton JT, Selective androgen receptor modulators (SARMs) negatively regulate triple-negative breast cancer growth and epithelial: mesenchymal stem cell signaling. *Plos One*, 2014; 9(7): 103-202.
27. Narayanan R, Coss CC, Dalton JT, Development of selective androgen receptor modulators (SARMs). *Mol Cell Endocrinol.*, 2018; 465: 134-142.
28. Narayanan R, Dalton JT, Androgen receptor: A complex therapeutic target for breast cancers. *Cancers (Basel)*, 2016, 8(12): 1-17.
29. Pantea-Stoian A, Pițuru SM, Hainăroşie R, Testosterone therapy, new opportunities in diabetes mellitus. *Farmacia*, 2018; 66(1): 1-7.
30. Papanicolaou DA, Ather SN, Zhu H, Zhou Y, Lutkiewicz J, Scott BB, Chandler J, A Phase IIa randomized, placebo-controlled clnical 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): 533-543
31. Perrenoud L, Schweizer Grundisch C, Baume N, Saugy M, Nicoli R, Risk of false positive results to SARM S-4 in case of therapeutic use of antineoplastic/ antiandrogen drug containing flutamide: a case study. *Drug Test Anal.*, 2016; 8(11-12): 1109-1113.
32. Ponnusamy S, Sullivan RD, Thiyagarajan T, Tillmann H, Getzenberg RH, Narayanan R, Tissue selective androgen receptor modulators (SARMs) increase pelvic floor muscle mass in ovariectomized mice. *J Cell Biochem.*, 2017; 118: 640-646.
33. Petering RC, Brooks NA, Testosterone therapy: Review of clinical applications. *Am Fam Physiciam.*, 2017; 96(7): 441-449.
34. Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED, Anabolic steroid–induced hypogonadism: diagnosis and treatment. *Fertil Steril.*, 2014; 101(5): 1271-1279.
35. Saitoh M, Ebner N, von Haehling S, Anker SD, Springer J, Therapeutic considerations of sarcopenia in heart failure patients. *Expert Rev Cardiovasc Ther.*, 2018; 16(2): 133-142.
36. Schragl KM, Forsdahl G, Gmeiner G, Enev VS, Gaertner P, Novel pathway for the synthesis of arylpropionamide-derived selective androgen receptor modulator (SARM) metabolites of andarine and ostarine. *Tetrahedron Lett.,* 2013; 54: 2239-2242.
37. Srinath R, Dobs A, Enobosarm (GTx-024, S-22): a potential treatment for cachexia. *Future Oncol.*, 2014; 10(2): 187-194.
38. Temerdashev AZ, Azaryan AA, Labutin AV, Dikunets MA, Zvereva IO, Podol'skii II, Berodze GT, Balabaev IA, Application of chromatography-mass spectrometry methods to the control of sport nutrition and medicines marketed via Internet. *J Anal Chem.*, 2017; 72(11): 1184-1192.
39. Thevis M, Piper T, Beuck S, Geyer H, Schänzer W, Expanding sports drug testing assays: mass spectrometric characterization of the selective androgen receptor modulator drug candidates RAD140 and ACP-105. *Rapid Commun Mass Spectrom.*, 2013; 27(11): 1173-1182.
40. Thevis M, Schänzer W, Detection of SARMs in doping control analysis. *Moll Cell Endocrinol.*, 2017; 1-12.
41. Thevis M, Schänzer W, Analytical approaches for the detection of emerging therapeutics and non-approved drugs in human doping controls. *J Pharma Biomed Anal.*, 2014; 101: 66-83.
42. Thevis M, Schänzer W, Synthetic anabolic agents: steroids and nonsteroidal selective androgen receptor modulators. *Handb Exp Pharmacol.*, 2010; 99-126.
43. Van Wagoner RM, Eichner A, Bhasin S, Deuster PA, Eichner D, Chemical composition and labeling of substances marketed as selective androgen receptor modulators and sold via the Internet. *JAMA*, 2017; 318(20): 2004-2010.
44. Vari CE, Ősz BE, Miklos A, Berbecaru-Iovan A, Tero-Vescan A, Aromatase inhibitors in men–off-label use, misuse, abuse and doping. *Farmacia*, 2016; 64(6): 813-818.
45. Vari CE, Ősz BE, Perian M, Măruşteri MS, Miklos A, Bosa P, Tero-Vescan A, Do aromatase inhibitors reduce fertility and impair sexual behaviour in an androgen doping model in rats?. *Farmacia*, 2017; 65(3): 336-342.
46. Wagels L, Votinov M, Kellermann T, Eisert A, Beyer C, Habel U1, Exogenous Testosterone Enhances the Reactivity to Social Provocation in Males. *Front Behav Neurosci.*, 2018; 12: 1-11.
47. Yatsu T, Kusakabe T, Kato K, Inouye Y, Nemoto K, Kanno Y, Selective androgen receptor modulator, YK11, up-regulates osteoblastic proliferation and differentiation in MC3T3-E1 cells. *Biol Pharm Bull.*, 2018; 41(3): 394-398.
48. ***World Anti-Doping Agency. The 2018 Prohibited List 2018. www.wada-ama.org.
49. ***World Anti-Doping Agency. World Anti-Doping Code, 2018. www.wada-ama.org.