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Selective Androgen Receptor Modulators (SARMs) in Sports: A Review

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Selective androgen receptor modulators (SARMs) are an exciting group of molecules with pronounced anabolic effects and very weak to missing androgenic ones. This is due to the tissue selectivity they possess and is their big advantage over anabolic androgenic steroids (AAS). As a result of this SARMs tend to be a big promise for improving the treatment process in different socially significant diseases such as osteoporosis, muscle wasting, benign prostatic hyperplasia, hypogonadism, sexual dysfunction, neurodegenerative diseases etc. SARMs are included in the prohibited list of World Anti-Doping agency (WADA) as they are a temptation for a lot of athletes regarding the exerted strong anabolic effect. However, as SARMs are freely available on the internet there are some reports for positive doping tests in professional sports connected with them. Still further research is needed to examine all the side effects of SARMs. Some of them may be harmful so both professional and amateur sportsmen, their coaches and doctors should be informed about this interesting topic.

Keywords: *SARM(s), anabolic effect, sports, doping, side effects*

Introduction

A very popular group of substances appropriate for misuse in sports are the anabolic androgenic steroids (AAS). AAS bind to the androgen receptor and perform strong anabolic effect due to which they increase the muscle mass and strength. Even though this can be an advantage in sports at the same time they pose risks concerning the health of their users. AAS have a strong androgenic effect which leads to a lot of side effects. In the last decades a number of side effects were described, some of them were irreversible. AAS increase the risk of severe myocardial damage, liver injury, testicular atrophy, menstrual disorders, hirsutism, psychological disorders, hematological alterations, clitoral hypertrophy, voice deepening and many others. At the end of the previous century a new class of molecules was discovered; the non-steroidal selective androgen receptor modulators (SARMs). They represent a new class of androgen receptor ligands that act similarly to anabolic steroids, but are selective in their effects, with anabolic predominance, and androgenic ones being relatively limited. This gives a number of advantages of SARMs over the anabolic androgenic steroids, associated with avoiding some of the side effects of the latter. Therefore, they can have a big impact on patients with a number of socially significant diseases, such as osteoporosis, benign prostatic hyperplasia, sarcopenia, neurodegenerative diseases

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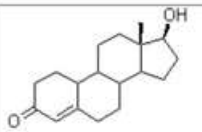
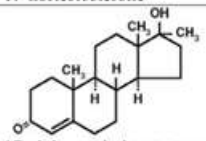
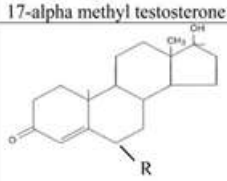
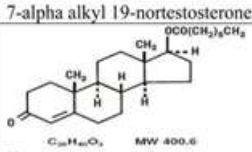
(Alzheimer's disease), sexual dysfunction, breast cancer, sarcopenia, various types of cachexia and hypogonadism (Chen et al. 2005a, Zhang and Sui 2013).

The selective androgen receptor modulators are commonly used in different sports to boost the physical performance and to increase athletic achievements due to the strong anabolic and weak androgenic effects. However, since 2008, they have been included in the list of prohibited substances of WADA, falling under the category of "other anabolic agents" in Section S1.2 of this list (Thevis and Schaenzer 2018). Even though there is currently no approved representative of SARMs as a drug by Food and Drug Administration (FDA), the substances are freely available on the internet. There is an evidence provided by the study of Van Wagoner et al. (2017) that only 52% of the 44 products offered online and tested contained real SARMs (Van Wagoner et al. 2017). There is a possibility the concentration of SARMs in the product to be different from the expected one, usually lower. Moreover, SARMs can be included as ingredients in different dietary supplements which poses a significant risk of giving a positive test during doping control in sports. In some cases, as a matter of fact, consumers can be tricked by masking the presence of SARMs on the label, using a coded one instead of the trade name of the representative (for example, MK-2866 or GTx-024 is indicated as an ingredient, instead of Ostarine). More control is needed on the trade with these substances on the internet and most importantly regarding the dosage. Very often the recommended dose is times higher than the effective one in clinical trials. Andarine and Ostarine are the most commonly used preparations from this group (Geyer et al. 2014). Various screening methods such as gas chromatography, liquid chromatography or mass spectrometry can be used during doping-control in sports to prove the misuse of SARMs. The presence of their metabolites can be easily detected in blood or urine specimens (Thevis et al. 2008a, Thevis et al. 2008b, Thevis et al. 2011). This leads to an increasing number of positive doping tests in professional athletes.

With regard to their chemical structure, SARMs can be divided into two main groups: steroidal and non-steroidal. The steroidal group of SARMs representatives were known as early as the middle of the last century (Bhasin and Jasuja 2009). The steroidal types of SARMs were obtained through structural changes in the molecule of testosterone. By removing the 19-methyl group, an increased anabolic effect of testosterone was achieved. Replacement of 7-alpha alkyl group reduced the interaction with the enzyme 5-α reductase and increased its tissue selectivity. Replacing the 17-alpha alkyl group increased the half-life of testosterone. The first non-steroidal SARMs were presented in 1998 and since then there has been a growing list of substances of this group, some of which are drug candidates and some of them are currently under clinical trials (Chen et al. 2005a). Non-steroidal SARMs are grouped into different classes: aryl propionamide analogues, bicyclic hydantoin analogues, quinolones, tetrahydroquinoline analogues, butanamides, benzimidazoles, tropanol derivatives, indole derivatives, thiophene derivatives and many others. The first discovered class was that of aryl propionamides. The number of representatives of the different classes is constantly increasing (Temerdashev and Dmitrieva 2020). Narayanan et al. (2008), Bhasin and Jasuja (2009) and Jasuja et al. (2012) represent very adequately the chemical structure of

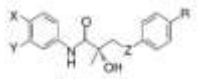
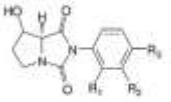
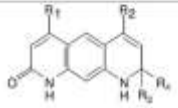
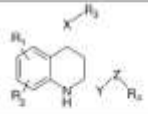
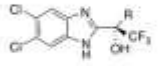
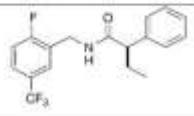
the two main groups of SARMs (Bhasin and Jasuja 2009, Jasuja et al. 2012, Narayanan et al. 2008) (see Tables 1 and 2).

Table 1. *Steroidal SARMs Structure*

Structure:Activity Relationship	Compounds	Chemical Structure
Removing 19 methyl increases anabolic activity	19-nor testosterone (nandrolone) series of compounds	 19-nortestosterone
17-alpha alkyl substitutions retard first-pass presystemic metabolism	Many orally active steroidal androgens have 17-alpha alkyl substitutions	 17-alpha methyl testosterone
7-alpha alkyl substitutions increase anabolic activity	7-alpha-methyl-19-nortestosterone	 7-alpha alkyl 19-nortestosterone
Esterification of 17-beta hydroxyl group increases hydrophobicity and extends duration of in vivo action	Testosterone enanthate, cypionate, and undecanoate	 Testosterone enanthate

Source: Bhasin and Jasuja 2009, Jasuja et al. 2012, Narayanan et al. 2008.

Table 2. *Non-Steroidal SARMs Structure*

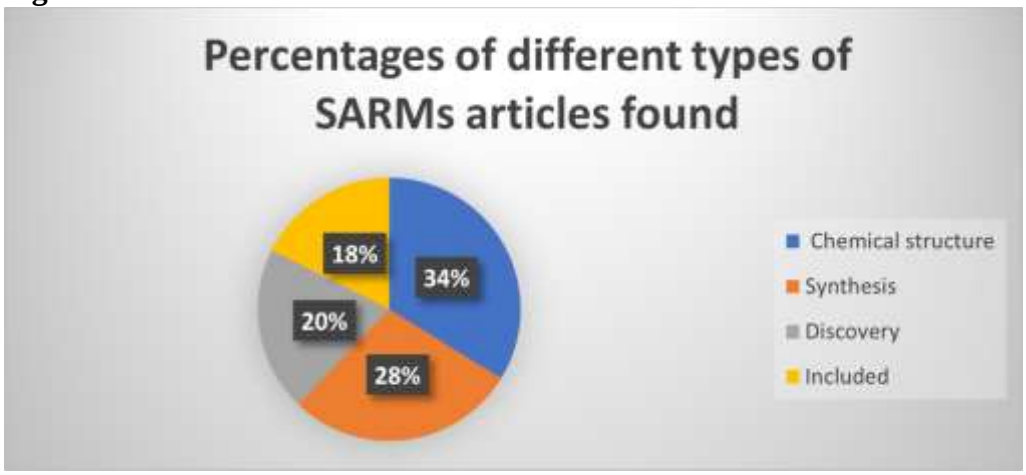
Chemotype	Structure	Examples
Aryl-propionamide analogs		Ostarine, andarine
Bicyclic hydantoin analogs		BMS-564929
Quinolinones		LGD-2226, LGD-2941
Tetrahydroquinoline analogs		Kaneh Pharmaceuticals, S-40503
Benzimidazoles		Johnson and Johnson's benzimadozole derivative
Butanamides		Merck SARM based on butanamide scaffold

Source: Bhasin and Jasuja 2009, Jasuja et al. 2012, Narayanan et al. 2008.

Materials and Methods

To be able to write this review we used different electronic databases such as Elsevier, Google Scholar, Science Direct, PubMed, etc. The main purpose of our article is to make sports professionals familiar with the presence of SARMs on the market and to increase their knowledge regarding the mechanism of action, usage of this group of substances, their potential risks and benefits and with the latest data concerning the doping control. In the literature we managed to find over 350 articles in English for the period between 1998-2021 years. There were some studies which were in different from English language, so we did not include them in our review. The terms we typed in the databases were 'selective androgen receptor modulators', 'SARM(s) and exercise', 'selective androgen receptor modulators rats', 'ostarine', 'ligandrol' 'SARMs doping', 'SARMs positive doping tests', 'SARMs rats'. The review is based on 60 articles. All the articles included were freely available for us. The main reason for an article not to be included in our review is that it does not provide the type of information we were looking for. For example, it gives detailed explanation about the chemical structure and development of SARMs and the process of their synthesis and discovery. As we already said this is not the focus of our review and such articles were considered irrelevant by us. The articles selection is presented in Figure 1.

Figure 1. *Articles Selection*



Results

Mechanism of Action

In order to exert their effects SARMs have to bind to the androgen receptor (AR) by genomic mechanism. AR is coded by a gene that is located on the X chromosome (Narayanan et al. 2018). AR is a transcription factor and consists of different domains. AR is located in the cytoplasm of the cell as its ligands are liposoluble and can pass through the cellular membrane. After the ligand binds to the receptor, initially, conformational changes in the receptor occur. The hormone-

receptor complex is formed and it moves to the cell nucleus. There, an interaction with the nuclear DNA will take place. Thus, AR may activate target genes that are involved in the regulation of various physiological processes. However, very important for its transcriptional activity is the group of proteins known as co-regulators. They are divided into two subgroups: co-activators which increase the transcriptional activity, and co-repressors which will decrease it. When DHT, testosterone or AAS bind to AR, the induced conformational change of the receptor leads to interaction with some co-regulators, and when SARMs bind to AR, the conformational change and co-activators with which AR interacts, are others (Narayanan et al. 2008, Narayanan et al. 2018). More than 200 co-regulators are known to activate or suppress various target genes. Other SARMs which can perform their effects by non-genomic mechanism also exist. Such representative is YK11. The mechanisms by which tissue selectivity of SARMs is achieved are not fully understood, but there are different hypotheses. Testosterone and anabolic androgenic steroids (AAS), under the action of the enzyme 5-α reductase, are converted into dihydrotestosterone (DHT) and other metabolites, which have greater biological activity and more pronounced effects on the genitals. In contrast SARMs are not susceptible to the action of this enzyme which helps to demonstrate their tissue selectivity (Gao et al. 2004). Another enzyme whose action is associated with side effects when taking AAS or testosterone is aromatase. It converts androgens into female sex hormones (estrogens), which are also responsible for the abovementioned side effects. Non-steroidal representatives of SARMs are not susceptible to the action of this enzyme as well (Bhasin 2015).

After binding to AR, DHT and SARMs increase the phosphorylating activity of various kinases (Bhasin and Jasuja 2009). Typically, a non-steroidal SARMs representative of the aryl propionamide class will mediate its effects through the following kinase pathways: MEK, ERK, p38 MAPK and others. While DHT uses the kinase pathways: PI3K, PKC, ERK and others (Narayanan et al. 2008). This shows that the two groups of ligands use different signaling pathways. The conformational change caused by the classical agonists of AR (testosterone or AAS) favours the classical intramolecular N-terminal/C-terminal interaction (N/C interaction). This interaction is essential for the selection of certain co-regulators, for the transcriptional activity of AR and for the modulation of target genes. In the synthesis of SARMs, the aim is to bring about a conformational change which does not stimulate this N-terminal/C-terminal interaction (N/C interaction).

Important Effects of SARMs

Effects on Bones

SARMs exert positive effects on bone tissue and its metabolism which is important for all sports. For example, Ostarine helped the formation of bone callus and healing of the bone after osteotomy. It increased the concentration of serum alkaline phosphatase, raised the serum level of phosphorus, and reduced the serum cholesterol level (Komrakova et al. 2020). Unlike Ostarine, the commonly used anabolic-androgenic steroid nandrolone decanoate induced femoral fracture in rats after an intake of twenty-seven days, stimulated to a less extent the formation of

callus and had no effect on the intact part of the bone (Guimarães et al. 2017). On the other hand, the selective androgen receptor modulator S-4 reduced the expected loss of bone substance in an osteoporosis model in rats maintaining bone mineral density and enhancing bone strength (Kearbey et al. 2007). In another study, in an osteopenic model in female rats, it was found that taking S-4 for 120 days after the ninetieth day following ovariectomy resulted in almost complete restoration of bone parameters compared to those of intact rats. Contrary to bone resorption, which was suppressed, bone anabolism was stimulated (Kearbey et al. 2009). Another modulator i.e., JNJ-28330835, also suppressed bone resorption (Allan et al. 2007). Again, in a model of osteoporosis in rats, the representative of tetrahydroquinolone analogues S-40503, after an intake of 4 weeks, led to an increase in the bone mineral density of the femur and the deposition of minerals in the periosteum of the same bone (Zhang and Sui 2013). This indicates the direct stimulating effect on bone formation of this SARM molecule (Hanada et al. 2003). The representative YK11 was able to stimulate the proliferation of MC3T3-E1 osteoblast cells in mice. YK11 also caused a significant increase in the specific markers for osteoblast differentiation osteoprotegerin (an inhibitor of osteoclastogenesis) and osteocalcin in comparison with the markers in untreated cells (Yatsu et al. 2018).

The combined application of the selective androgen receptor modulator LGD-3304 with a representative of bisphosphonates (alendronate) led to the potentiation of the effects of both substances and obtained a better total effect which is suitable for the treatment of osteoporosis (Vajda et al. 2009). S-101479 enhanced the activity of the alkaline phosphatase, the transcriptional activity of the androgen receptors in the osteoblast cell line and increased the bone mineral density without stimulating the proliferation of the endometrium in an osteopenic model in female rats (Furuya et al. 2013). Another study, once again in an osteopenic model in rats, compared the effects of S-101479 with other drugs for treatment of osteoporosis: bisphosphonates, selective estrogen receptor modulators (SERMs) and synthetic analogues of parathyroid hormone. All substances increased the bone mineral density. Only S-101479 increased the size of the bone. Potentiation of their effects was observed in combined application (Furuya et al. 2012). The preparation 4c had an osteoanabolic effect in female rats with induced osteoporosis and had a sparing effect on uterus compared with DHT (Nagata et al. 2011). Another representative of SARMs, i.e., 1d, also used in a model of osteoporosis in female rats, increased the bone mineral density of the femur, without any side effects on the uterus and the clitoris (Nagata et al. 2014). LGD2226 is also a non-steroidal representative of SARMs, which prevented a decrease in bone density, suppressed the bone resorption and stimulated bone formation in an osteopenic model in rats (Rosen and Negro-Vilar 2002). Some of the carboranes which are carbon-containing compounds, derivatives of the chemical element boron, may have effects on bone tissue such as those of SARMs. It was found that the representative of this group, BA321, restored the lost bone density in castrated male and female rats. In male rats, it increased the weight of the seminal vesicles, and in females reduced the induced atrophy of the uterus (Watanabe et al. 2016).

Effects on Muscles

SARMs also have a number of pronounced beneficial effects on muscle tissue what ranks them among the candidates for the treatment of cachexia and sarcopenia of various origin and for misuse in sports as well. In the literature there are several effects of YK11. For example, it activated AR without performing the N/C-terminal interaction, induced the differentiation of the C2C12 myoblast cell line. DHT demonstrated the same effect, but YK11 more effectively induced the key myogenic regulatory factors (myogenic differentiation factor, myogenic factor 5, and myogenin). YK11 also stimulated the expression of follistatin, which plays a major role in the realization of YK11-mediated myogenic differentiation (Kanno et al. 2013). The JNJ28330835 modulator, alternately, reduced by half the loss of lean body mass caused by orchidectomy in rats. It also mediated the restoration of 30% of the already lost muscle body mass in older castrated rats and stimulated the growth of m. levator ani (Allan et al. 2007). JNJ 37654032 is a similar agent with identical effects (Allan et al. 2008), and the MK-4541 modulator preserved lean body mass in female rats after ovariectomy (Chisamore et al. 2016). The administration of glucocorticoids or hypogonadism can cause muscle atrophy in rats, but the disease may be favourably affected by the intake of SARMs. The atrophy is a result of the enhanced expression of MAFbx and MuRF1, which are ubiquitin ligases and form a part of the ubiquitin proteasome system that is responsible for the decomposition of proteins and the decreased IGF-I function. SARMs inhibited the activity of the ubiquitin ligases and enhanced that of IGF-I (Jones et al. 2010). In a model of muscle atrophy in mice, GLPG0492 partially prevented the development of atrophy and caused hypertrophy of muscle fibers in a dose-dependent manner. The efficiency of the SARMs representative in this model is comparable to that of testosterone propionate, and the effect is achieved by affecting the signal pathways which regulate the homeostasis of the muscles (Blanqué et al. 2014).

Ostarine (S-22), which is the field leader of SARMs, was able to reduce muscle loss and to decrease the total fat percentage, with minimal side effects on the prostate (Zilbermint and Dobs 2009). In a double-blind study in postmenopausal women and older men, Ostarine increased lean body mass and also had a favourable effect on insulin resistance. Similarly, to the other selective modulators, in a study in postmenopausal women and men over the age of forty-five, Ostarine caused a significant increase in the reduced lean body mass (Dobs et al. 2013). An increase in muscle strength and endurance in mice treated with the GLPG0492 modulator was observed in a Duchenne muscular dystrophy model (Cozzoli et al. 2103). The intake of MK-0773 for a period of 6 months by 170 women with sarcopenia led to a significant increase in muscle mass and physical strength (Papanicolaou et al. 2013). The transdermal modulator (LY305) restored the muscle mass in a model of muscle atrophy in test animals. Moreover, this modulator did not cause significant changes in the values of hematocrit and high-density lipoproteins (HDL) (Krishnan et al. 2018). Another non-steroidal SARM that is considered suitable for the treatment of sarcopenia and cachexia is SARM2f. It was used in various models of malignant cachexia in rats and restored the body mass as well as increased the weight of m. levator ani without enlarging

the prostate or seminal vesicles (Morimoto et al. 2017). SARM2f demonstrated its anabolic effects in muscle tissue and decreased the lipid levels in monkeys as well (Morimoto et al. 2020). The rate of fractional synthesis of proteins from different muscles on the tenth day of administration of selective androgen receptor modulators can be measured and may provide early biomarkers for determining the expected increase of lean body mass and muscle weight of the corresponding muscles (Shankaran et al. 2016).

Effects on Nervous System

SARMs are believed to have a neuroprotective effect. For example, RAD140 also known as testolone delayed the programmed nerve cell death in various neurodegenerative models in rats. The mechanisms of this neuroprotective effect were related to MAPK (mitogen-activated protein kinase) - signal pathways (Jayaraman et al. 2014). It can be speculated that this effect of RAD140 could be used in the treatment of Alzheimer's and other neurodegenerative diseases. The selective androgen receptor modulators also have a favourable effect on age-related cognitive deficit. It is assumed that they increased the levels of androgen receptors in our brain and had an antagonistic effect on disorders of hippocampus-dependent exploration of new locations (Acevedo et al. 2008). Moreover, in mice, the selective androgen receptor modulator AC-105 improved the condition of anxiety. If AC-105 is used in combination with the selective estrogen receptor modulator (SERM) - AC-186, it enhances the activity of amyloid-β degrading enzymes, thus reducing the concentration of this group of peptides that are strongly associated with the development of Alzheimer's disease. Another effect of the combined application of these substances was the improvement of cognitive abilities and elevated levels of AR in the brain. This suggests that such a combination could be used in the treatment of patients with Alzheimer's disease (George et al. 2013). NEP 28 is another representative of SARMs, which in addition to its favourable effects on bone and muscle tissue, also had a neuroprotective effect (Akita et al. 2013).

SARMs and Positive Doping Tests

As SARMs are freely available for everyone on the Internet professional athletes can purchase them as well. Already there are reports for positive doping tests due to the use of different representatives of SARMs in professional sports. The number of positive tests increased since the year 2010. For example, the professional basketball player Joakim Noah who played for more than a decade in NBA (National Basketball Association) tested positive with the representative Ligandrol (LGD-4033) in 2017. He was completely cooperative during the investigation, and it was accepted that the positive result occurred due to an unintentional use. This is very likely to be true because SARMs are present in different dietary supplements without their presence being announced. In the end the player was suspended for twenty matches (Cacciola and Vorkunov 2017). Another case of positive doping tests occurred in the UFC (Ultimate Fighting Championship) in 2018. The forbidden substance found after the doping tests was

the aryl-propionamide analogue Ostarine. The following athletes were suspended: Augusto Mendes, 36, of Glendale, Ariz., tested positive for ostarine following an out-of-competition test conducted on March 7, 2018; Marvin Vettori, 25, of Mezzocorona, Italy, tested positive for ostarine following an out-of-competition test conducted on August 6, 2018; Sean O'Malley, 24, of Phoenix, Ariz., tested positive for ostarine following out-of-competition tests conducted on September 5, 2018 and December 8, 2018; Nicco Montano, 30, of Albuquerque, N.M., tested positive for ostarine following an out-of-competition test conducted on October 25, 2018. They duration of the suspension for all of them was 6 months. Similarly, to the case with Joakim Noah the reason for SARMs intake may be the use of contaminated dietary supplements. Sports professionals should be very careful when using dietary supplements and should pay a lot of attention when reading the constituents. Otherwise, they can suffer an unexpected suspension (USADA 2019). A list with the different names of SARMs to look for on the label of a supplement is provided by Van Wagoner et al. (2017) (see references).

The Jamaican 400m runner Bobby-Gaye Wilkins was banned for two years after using a performance-enhancing substance. Wilkins tested positive for the banned substance andarine (S4, GTx-007) at the world indoor championships in Doha, Qatar, in March 2010. The Russian athletes Svetlana Denyaeva-Biryukova, Roman Semakin, Nadezhda Mokeeva, Tatyana Dektyareva and Irina Yumanova all served a 2-year ban by IAAF (International Association of Athletics Federations) after respresentatives of SARMs or their metabolites were found in their doping samples. The hurdling professional Thomas Goller served as well a 2-year ban by IAAF from 2010 to 2012 for using selective androgen receptor modulators. Azerbaijan's Ethiopian-born 3,000 meters steeplechase winner Chaltu Beji turned positive during a doping test at the athletics competition in Baku, 2015. Beji provided urine sample which contained the banned anabolic agent ostarine. Further testing at the World Anti-Doping Agency-accredited laboratory in Moscow followed. A B-sample was requested following the initial failure, but the result again showed traces of the product (Butler 2015). According to WADA coaches actively involved in doping can be banned. Rules in the new code also seek to drive the nonconforming coaches out of the sport by giving athletes a stronger incentive not to work with them. Moreover, there can be sanctions for athletes that associate with coaches or support personnel serving a ban. Such was the case with former University of Virginia coach Martin Maric, who tested positive himself (with ostarine) and put not only himself at risk by coaching while serving a doping suspension, but also his athletes.

Up to now the number of positive doping tests due to AAS usage remains a lot higher than the number of positive tests after SARMs detection. Nowadays the most appropriate methods for detecting the presence of SARMs during doping control in different specimens (urine or blood plasma) are liquid chromatography, mass spectrometry or liquid chromatography tandem mass spectrometry. Liquid chromatography coupled with mass spectrometry (LC-MS) is an advanced method used in many clinical laboratories because of the many advantages it possesses. Some of them include detecting molecules in extremely low concentrations (in picograms per milliliter (pg/mL)), very high sensitivity, specificity, short analysis

times. Although there are a lot of studies on LC-MS or GC-MS (gas chromatography-mass spectrometry), it seems that they should still be optimized to avoid the false positive results due to the structural similarity of active metabolites of SARMs with androgen receptor antagonists such as flutamide (Perrenoud et al. 2016). There was a case report regarding an in-competition female athlete urine sample, in which metabolites of S-4 were detected, proving that the athlete used andarine for better physical performance (Miklos et al. 2018).

SARMs and Their Side Effects

The knowledge for SARMs up to now still makes them an attractive future option in the treatment of a great number of diseases, such as osteoporosis, cachexia, sarcopenia, benign prostatic hyperplasia, neurological diseases with cognitive deficits, hypogonadism, sexual dysfunction, breast cancer and option for effective contraception in men. On the other hand, their use, including by athletes, is associated with a number of adverse side effects (Geyer et al. 2014). However, most of them are of low frequency and reversible. The most common side effects are related to elevated liver enzymes and changes in various lipid fractions. There is still insufficient data on what the side effects of SARMs would be in the long-term use. Despite this fact SARMs are thought to be far more sparing than AAS. AAS provoke responses from the body which very often significantly reduce the quality of life. Some of them can be even fatal. What do we know about the side effects of SARMs in healthy individuals and in experimental models with animals or humans up to now? For example, after an intake of LGD 4033 for 21 days by healthy men the following adverse side effects were reported: a decrease of plasma levels of the sex hormone binding globulin (SHBG), triglycerides, HDL and FSH (Basaria et al. 2013). The changes found were manageable, with lipid and hormone concentrations returning to normal after discontinuation of the intake of LGD-4033. Administration for 2 weeks of the selective androgen receptor modulator C-6 in intact rats caused a decrease in gonadotropic hormone and serum testosterone levels. Later during the experiment, after the tenth week, a suppression of spermatogenesis occurred as well (Chen et al. 2005b).

In a postmenopausal model of osteoporosis in female rats, GTx-024 caused uterine weight gain and increased plasma phosphorus concentration (Hoffmann et al. 2019). Adverse side effects observed after Ostarine intake in humans included febrile neutropenia, pneumonia and progression of a present malignant disease (Dobs et al. 2013). Ostarine is the representative with the highest number of clinical trials performed. In a large-scale experiment with women who suffer from sarcopenia, it was reported that the intake of MK-0773 did not cause androgenization, but in some of the respondents, there was, albeit transient, an increase in transaminase liver enzymes (Papanicolaou et al. 2013). Another study reported that in healthy men and postmenopausal women the administration of GSK2881078 caused a decrease in HDL and SHBG. In women, these effects occurred even at lower doses than in men. One woman was reported to have a rash, and two men had elevated creatine phosphokinase levels after physical exercise (Clark et al. 2017). The selective modulator RAD140, in various in vivo

and in vitro models, was found to cause decreased appetite and weight, elevated liver enzymes (AST and ALT), as well as hypophosphatemia (Hamilton et al. 2019). After the application of the new representative of SARM - PF-06260414 in healthy people of different ethnics (Japanese and humans from countries of the West), the tolerance of the preparation was good, but there were slight adverse effects, such as headache and increased ALT levels (Bhattacharya et al. 2016).

Several case reports about liver injury due to SARMs intake are available in the literature. For instance, a 32-year-old man had a daily intake of 10 mg of Ligandrol (LGD-4033) for 2 weeks in order to increase his muscle mass. He was hospitalized. The main reasons for the hospitalization were elevated liver enzymes and presence of jaundice. Some of the laboratory results were the following: aspartate aminotransferase 91 IU/L, alanine aminotransferase 229 IU/L, alkaline phosphatase 88 IU/L, total bilirubin 2.4 mg/dL. Other symptoms included fatigue, pruritus, and weight loss. In the hospital magnetic resonance cholangiopancreatogram was performed and a small hepatic cyst and splenomegaly were found. A result from liver biopsy revealed cholestatic hepatitis, portal, periportal and perisinusoidal fibrosis. No information about liver problems was present in the medical, social, surgical, and family history of the man. Hepatitis A, B, and C markers were negative and the conclusion of the physicians was DILI (drug induced liver injury) by the Ligandrol intake. The patient remained in hospital for 24 hours and was prescribed appropriate drugs. We have to bear in mind the fact that the dosage used by this young man was many times higher than the SARMs clinically effective dosages usually used in human trials and experimental animal models (0.1 mg, 0.3 mg, and 1.0 mg) (Barbara et al. 2020).

Another interesting case report stated that a 24-yaer old man developed anorexia, jaundice, wight loss (around 5 kg) and nausea. This was the consequence of an intake of Ligandrol (LGD-4033) capsules for a period of 9 weeks as a gym supplement. Some of the elevated parameters connected with the liver included: bilirubin, 116μmol/L (reference, <30); alanine aminotransferase (ALT), 273 U/L (reference, <45); aspartate aminotransferase (AST), 111 U/L (reference, <45); alkaline phosphatase (ALP), 289 U/L (reference, <100). Liver tests normalized after a period of 4 months (Flores et al. 2020). There was no information concerning the dosage of LGD-4033 used but binge drinking once a month was documented. Third case report described a 49-year-old man presented with jaundice and itching of 5 weeks duration. He regularly took an antidepressant (venlafaxine) for 11 months. Four months before the symptoms have occurred the man used RAD-140 (testolone) for 4 weeks followed by an intermittent use thereafter. Investigations showed the following: bilirubin, 291 μmol/L; ALT, 54 U/L; AST, 59 U/L; ALP, 327 U/L. There was no significant alcohol consumption. Biliary obstruction and other possible liver diseases were excluded. Liver histology results showed moderate cholestasis with ductopenia and minimal fibrosis and inflammation, consistent with drug-induced liver injury. All liver tests of the 49-year-old-man were normal when examined 12 months later (Flores et al. 2020). Once again, no information was given in this case report about the dosage of testolone used.

The risk of severe liver injury mostly depends on the dose used. Doses around 10 to 100 times higher than the ones used in clinical trials are highly likely to increase the risk. Otherwise, according to our knowledge, when the intake of SARMs is of the appropriate dose the side effects concerning the liver are very weak and quickly reversible. One possibility to escape the adverse effects on the liver can be the use of transdermal SARMs like LY305. This route of administration limits the exposure of the liver to selective androgen receptor modulators. One of the difficulties in determining the side effects of selective androgen receptor modulators in clinical trials is connected with ethics. This is due to the fact that very high dosages should be given to the volunteers in order to match the ones used in doping or by amateurs going to the gym.

Conclusions

SARMs are a class of molecules which gives us hope for the future. Holding the big advantage of tissue selectivity over AAS and their derivatives, SARMs can be a potential treatment for many socially significant diseases like amyotrophic lateral sclerosis, dermatomyositis, osteoporosis, breast cancer, sarcopenia, various types of cachexia, benign prostatic hyperplasia, hypogonadism, neurodegenerative diseases (Alzheimer's disease), stress urinary incontinence (SUI). SARMs have well-pronounced anabolic effects in bones and muscles and sparing androgenic effects in the prostate and seminal vesicles. However, as there is no approved representative of SARMs by the FDA, we still need further investigation about the side effects of these substances (their frequency, severity and reversibility as well). Further information is needed and about the extent of improvements of different important body functions SARMs can give us. Some clinical trials with SARMs have been terminated due to lack of efficacy, others were completed and already have results or still await them. Probably in the near future there will be more clinical trials to come. The selective modulators are a temptation in sports due to their strong anabolic effect enhancing the physical performance. Nevertheless, SARMs are included in the prohibited list of WADA and a significant number of positive doping tests in different types of sports were revealed. The selective modulators pose a threat to all sportsmen especially to amateurs who buy SARMs on their own from the internet, do not consult a doctor and are not familiar with the correct dosage for intake. So no matter if you are an amateur or a sports professional, a coach or a sports medicine doctor, if you are involved in sports it is better to be aware of the possible benefits and risks of SARMs.

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