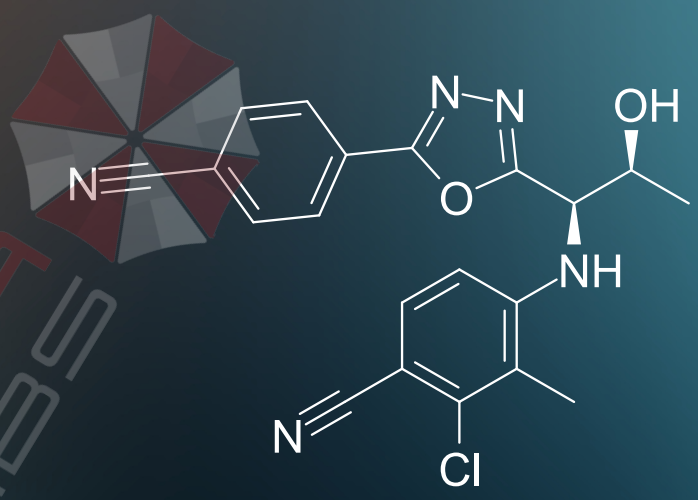

RAD-140 (Vosilasarm) - Emerging Research and Clinical Insights

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History

Vosilasarm is part of the relatively novel family of selective androgen receptor modulators (SARMs). This class has been proposed to be promising both for medical application but also for performance enhancement in athletes. Unlike classical steroids, SARMs have fewer side effects, but still retain anabolic activity. In addition, androgens are problematic to administer orally, because they suffer from a massive first-pass effect and damage the liver at the same time. SARMs have two main advantages: They usually do not have any hepatotoxic effects, but they also have fewer side effects connected their direct activation of androgen receptors (e.g. acne, prostate growth or hair loss/ growth in unwanted areas), because SARMs only activate specific subsets of the androgen receptor (like androgen receptors in skeletal muscle to promote growth). More specifically, they have the potential to increase muscle mass and performance, which is why SARM as tested to be used against Cachexia and age related muscle loss, without the problematic side effects of androgens like testosterone. In the case of Vosilasarm was found to have anabolic effects in muscle, but has a comparatively weak effect on prostate and seminal vesicle tissue.

Vosilasarm was likely developed since the mid to late 2000`s by Radius Health (development name: RAD-140) and was first mentioned in the literature in 2010. Later Ellipses Pharma was in charge of development (development name: EP0062). It is also sometimes referred to as Testolone or Testalone. In the majority of literature, it is still referred to as RAD-140. The first clinical study began in 2017 on women with stage IV breast cancer (NCT03088527). A further clinical trial is in progress as of 2024 (NCT05573126).[1]

Vosilasarm is listed under the World Anti-Doping Agency list of prohibited substances, due to its postulated effects on skeletal muscle growth.

Preclinical Trials

In the first published document of vosilasarm, the authors described its synthesis and experiments on rats and monkeys. The oral bioavailability was high (up to 75 %) and the stability against microsomal degradation, the half-life exceeded 2 hours. The first effects on muscle tissue in castrated rats were observed with a dose of 0.03 mg/kg bodyweight and reached equivalent levels of not castrated individuals at a dose of 0.3 mg/kg. Androgen receptor affinity was found to be 30 %

higher compared to the strongest endogenous androgen dihydrotestosterone (Ki = 7 nM vs 10 nM). Vosilasarm was however not able to stimulate the prostate or the seminal vesicles in a comparable way to testosterone. If testosterone and vosilasarm (10 mg/kg) were co-administered, vosilasarm reduced the effect of testosterone on the seminal vesicle, but added to the anabolic activity in muscle. Finally, the authors showed that vosilasarm increases the lean body mass in young, male cynomolgus monkeys in a concentration dependent manner from 0.01 mg/kg to 1 mg/kg. This highlighted the potential of vosilasarm in aiding skeletal muscle growth.[2] In a later comparison of three SARMs (GSK- 2881078 and GLPG0492 and Vosilasarm), it was reported that Vosilasarm has the highest binding affinity to the human androgen receptor amongst those three.[3]

Contrary to previous findings, a recent study from 2023 has reported no effect of Vosilasarm (5 mg/kg) on muscle strength in female mice for 10 weeks. Supplementation also increased frailty status and mortality risk in the young and adult treated groups compared to the controls.[4] Another data set showed an increase on muscle mass in rats, but not above statistical significance.[5]

A further preclinical observation showed that the androgen receptors expressed in breast cancer are sensitive to vosilasarm. Other than in muscles, the activation of the androgen receptor inhibits the growth of breast tissue, which then leads to a reduced tumor mass. The co-administration of vosilasarm and palbociclib (an anti-tumor agent) improved the tumor inhibiting effect.[6] A mouse model of breast cancer later has showed that vosilasarm led to a 80 % growth reduction of the cancer.[7]

Classical androgens are known to have neuroprotective effects and their impact on the brain has been researched extensively. A study on rats hence has focused on the neurological impact of vosilasarm. Indeed, vosilasarm was found to protect neurons from cell death in cell culture and in living rats against the neurotoxin kainate. The findings demonstrated initial preclinical efficacy in neuroprotective actions relevant to Alzheimer's disease and related neurodegenerative diseases.[8] However, this aspect of vosilasarm has not been explored further by subsequent studies to this day.

The metabolites of vosilasarm in human liver has been investigated recently in 2023 using mass spectrometry. In human urine metabolites that mostly correspond to oxidation and conjugation with glucuronic acid were detected, which corresponds to regular liver phase 1 and 2 metabolism.[9] In horses, sulfation of Vosilasarm was also described as a possible metabolic pathway.[10]

Clinical Trials & Reports

The first human phase 1 study characterized the safety, tolerability, maximum tolerated dose, pharmacokinetic profile and antitumor activity of vosilasarm. The study was conducted with 22 postmenopausal women with stage IV breast cancer. Vosilasarm was administered in doses of 50, 100, and 150 mg daily. The most common side effects were elevation in liver enzymes (~ 50 %) and bilirubin, vomiting, dehydration and decreased appetite (each 27% of participants). Plasma half-life of vosilasarm was 44.7 hours. One of the patients showed a partial tumor response to administration.

It was also found that sex hormone-binding globulin (SHBG) decreased significantly in all patients. These results showed an acceptable safety profile given the therapeutic setting and confirmed that vosilasarm may be used as second- or third-line treatment in certain types of breast cancer.[11]

Currently, another phase clinical trial is ongoing for approximately 40 women with hormone receptor positive breast cancer and no available standard treatment. It is planned to examine the safety of side effects of escalating doses of Vosilasarm in this group. The trial is expected to end in the first quarter of 2025.[12]

A case report on a 24-year-old male which had been taking vosilasarm for 5 weeks highlights the potential liver toxicity of the compound, which was already observed in the first clinical study. The patient presented with abdominal pain, jaundice, pruritus and clear signs of liver damage in bloodwork and histology. Symptoms and liver injury resolved after cessation of the offending agent. A similar clinical

case was reported with a 52-year-old male taking both vosilasarm and LGD 4033 (another SARM) simultaneously. Liver enzymes returned to normal levels approximately 3 months after the patient stopped both supplements.[13] Similar cases were reported in 26-year-old Caucasian male in Florida,[14] a 24-year-old Asian male,[15] a 30-year-old from California,[16] and a 21-year-old male from the Maldives.[17]

An additional case report has described acute myocarditis in a 32-year-old male self-medicating with vosilasarm. The patient recovered quickly after treatment and discontinuing self-administration of the compound, he was discharged 8 days after hospitalization. This is the only case reported so far indicating cardiological complications.[18] Hence it is not clear if it is linked to vosilasarm intake or if it is a purely incidental case.

Detection

Since Vosilasarm is part of the World Anti-Doping Agency list of prohibited substances, there are some studies focusing specifically on how to detect it from human samples. The detection methods include LC-MS/MS from human urine.[19] and detection from serum using specialized nanoparticles.[20] New in the field of anti-doping is a proteomics based approach that identifies not the drug or its metabolites, but the altered protein expression pattern caused by the compound.[21] This approach may also be able to target other SARMs using the same method.

Conclusion

The available information so far points to the conclusion that Vosilasarm likely, much like other SARMs, positively affects muscle growth and performance in humans. This is however not supported by human trials, since human data so far is only available for breast cancer patients with otherwise treatment resistant forms of breast cancer.

Research highlights the importance of monitoring liver health when using vosilasarm, with several case reports indicating that some men have experienced reversible changes in liver function. These instances were closely observed, and fortunately, all affected individuals saw a full recovery after a brief period of discontinuing vosilasarm. It's noteworthy that these occurrences appear to be rare and may primarily affect those with certain genetic predispositions or who consume higher doses.

References

[1] Lim E, Hamilton E, Palmieri C, Arkenau H-T, Brook S, Fisher G, Mazur A. Abstract OT1-02-02: A phase 1/2 study to evaluate the safety and efficacy of EP0062, an oral Selective Androgen Receptor Modulator (SARM), for the treatment of AR+/HER2-/ER+ advanced breast cancer. *Cancer Research*. **2023**;83:OT1-02-02-OT1-02-02. doi: 10.1158/1538-7445.SABCS22-OT1-02-02.

[2] Miller CP, Shomali M, Lyttle CR, O'Dea LSL, Herendeen H, Gallacher K, Paquin D, Compton DR, Sahoo B, Kerrigan SA, et al. Design, Synthesis, and Preclinical Characterization of the Selective Androgen Receptor Modulator (SARM) RAD140. *ACS Med Chem Lett.* **2011**;2:124–129. doi: 10.1021/ml1002508.

[3] Zierau O, Kolodziejczyk A, Vollmer G, Machalz D, Wolber G, Thieme D, Keiler AM. Comparison of the three SARMs RAD-140, GLPG0492 and GSK-2881078 in two different in vitro bioassays, and in an in silico androgen receptor binding assay. *J Steroid Biochem Mol Biol.* **2019**;189:81–86. doi: 10.1016/j.jsbmb.2019.02.014.

[4] Brown AM, Ganjayi MS, Baumann CW. RAD140 (Testolone) negatively impacts skeletal muscle adaptation, frailty status and mortality risk in female mice. *Clin Exp Pharmacol Physiol.* **2023**;50:973–983. doi: 10.1111/1440-1681.13824.

[5] Puskas J. Pre-clinical assessment of the selective androgen receptor modulator RAD140 to increase muscle mass and bone mineral density.

[6] Yu Z, He S, Wang D, Patel HK, Miller CP, Brown JL, Hattersley G, Saeh JC. Selective Androgen Receptor Modulator RAD140 Inhibits the Growth of Androgen/Estrogen Receptor-Positive Breast Cancer Models with a Distinct Mechanism of Action. *Clin Cancer Res.* **2017**;23:7608– 7620. doi: 10.1158/1078-0432.CCR-17-0670.

[7] He S, Conlan MG, Arlt H, Morris C, Yu Z. Abstract P5-05-01: Novel mechanisms of action of selective androgen receptor modulator RAD140 in AR+/ER+ breast cancer models. *Cancer Research*. **2020**;80:P5-05-01-P5-05-01. doi: 10.1158/1538-7445.SABCS19-P5-05-01.

[8] 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. *Endocrinology*. **2014**;155:1398–1406. doi: 10.1210/en.2013-1725.

[9] Wagener F, Naumann N, Göldner V, Görgens C, Guddat S, Karst U, Thevis M. Comparison of in vitro approaches for predicting the metabolism of the selective androgen receptor modulator RAD140. *Anal Bioanal Chem*. **2023**;415:5657–5669. doi: 10.1007/s00216-023-04835-z.

[10] So Y-M, Wong JKY, Choi TLS, Prabhu A, Stewart B, Farrington AF, Robinson P, Wan TSM, Ho ENM. Metabolic studies of selective androgen receptor modulators RAD140 and S-23 in horses. *Drug Test Anal*. **2021**;13:318–337. doi: 10.1002/dta.2920.

[11] LoRusso P, Hamilton E, Ma C, Vidula N, Bagley RG, Troy S, Annett M, Yu Z, Conlan MG, Weise A. A First-in-Human Phase 1 Study of a Novel Selective Androgen Receptor Modulator (SARM), RAD140, in ER+/HER2- Metastatic Breast Cancer. Clin Breast Cancer. 2022;22:67–77. doi: 10.1016/j.clbc.2021.08.003.

[12] Hamilton E, Vidula N, Ma C, LoRusso P, Saeh J, Reichert V, Yu Z, Annett M, Weitzman A, Hattersly G, et al. Abstract OT1-02-02: A phase 1, first-in-human, multi-part study of RAD140, an oral nonsteroidal selective androgen receptor modulator, in postmenopausal women with hormone receptor positive breast cancer. *Cancer Research*. **2019**;79:OT1-02-02-OT1-02-02. doi: 10.1158/1538-7445.SABCS18-OT1-02-02.

[13] Barbara M, Dhingra S, Mindikoglu AL. Drug-Induced Liver Injury Associated With Alpha Bolic (RAD-140) and Alpha Elite (RAD-140 and LGD-4033). *ACG Case Rep J.* **2020**;7:e00409. doi: 10.14309/crj.0000000000000409.

[14] Ladna M, Taylor K, Bhat A, Dideban B. Idiosyncratic drug-induced liver injury related to use of novel selective androgen receptor modulator RAD140 (Testalone): a case report. *J Med Case Rep.* **2023**;17:134. doi: 10.1186/s13256-023-03847-8.

[15] Yaramada P, Goyal P, Hammami M, Cai C. S2399 RAD-140: An Emerging Cause of Drug-Induced Liver Injury. *Am J Gastroenterol.* **2020**;115:S1273-S1273. doi: 10.14309/01.ajg.0000711644.40417.60.

[16] Pazevic A, Pak K, Bachmann A, Sadowski B. S3537 Harm From SARMs: RAD-140, A Selective Androgen Receptor Modulator Leading to Acute Liver Injury. *Am J Gastroenterol.* **2023**;118:S2314-S2314. doi: 10.14309/01.ajg.0000963788.30519.9e.

[17] Shashank Bhattarai1, Sandip Raj Pradhan2*. Oral Androgenic Supplement RAD140 Induced Acute Liver Injury- A Case Report. 2023. doi: 10.5281/ZENODO.8286702.

[18] Padappayil RP, Chandini Arjun A, Vivar Acosta J, Ghali W, Mughal MS. Acute Myocarditis From the Use of Selective Androgen Receptor Modulator (SARM) RAD-140 (Testolone). *Cureus.* **2022**;14:e21663. doi: 10.7759/cureus.21663.

[19] Wagener F, Euler L, Görgens C, Guddat S, Thevis M. Human In Vivo Metabolism and Elimination Behavior of Micro-Dosed Selective Androgen Receptor Modulator RAD140 for Doping Control Purposes. *Metabolites*. **2022**;12. doi: 10.3390/metabo12070666.

[20] Henderson A, Sullivan MV, Hand RA, Turner NW. Detection of selective androgen receptor modulators (SARMs) in serum using a molecularly imprinted nanoparticle surface plasmon resonance sensor. *J Mater Chem B.* **2022**;10:6792–6799. doi: 10.1039/D2TB00270A.

[21] Cheung HW, Wong K-S, To NS, Bond AJ, Farrington AF, Prabhu A, Curl P, Wan TSM, Ho ENM. Label-free proteomics for

discovering biomarker candidates of RAD140 administration to castrated horses. *Drug Test Anal.* **2021**;13:1034–1047. doi: 10.1002/dta.2988.

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