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Review Article

Selective Androgen Receptor Modulators: An Emerging Liver Toxin

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Abstract

Selective androgen receptor modulators (SARMs) are a class of nonsteroidal drugs that are favored over anabolic androgenic steroids (AASs) for their tissue-selectivity and improved side-effect profile. These drugs have been evaluated for treatment of various diseases including muscle-wasting disorders, osteoporosis, and breast cancer. Despite lacking approval for therapeutic use, SARMs are widely used recreationally as performance enhancing drugs by bodybuilders and athletes. In recent years, cases of drug-induced liver injury (DILI) secondary to SARMs have begun to emerge, but little is known regarding their hepatotoxicity. In this review, we provide current knowledge regarding DILI from SARMs. A literature search was conducted regarding SARMs and liver injury to evaluate relevant cases and information. SARMs have been associated with a cholestatic syndrome congruent with that of DILI from AASs, and it consists of a bland cholestasis in which there is minimal bile duct injury, inflammation, or necrosis. Patients present with an insidious onset of jaundice with marked hyperbilirubinemia and mild hepatic enzyme elevations. No clear treatment exists, although patients typically show improvement with cessation of the offending SARM. Given the novelty of these drugs, further study is necessary to understand diagnosis, management, and complications of SARM-related DILI.

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Introduction

Selective androgen receptor modulators (SARMs) are a class of nonsteroidal drugs that selectively bind to the androgen receptor. These tissue-selective drugs are intended to have similar anabolic effects as that of anabolic androgenic steroids (AASs) but with an improved safety profile and reduced androgenic side effects. Since their development, SARMs have been investigated for a wide variety of clinical applications including muscle-wasting diseases, osteoporosis, and breast cancer.[1]

These drugs offer greater therapeutic promise than AASs because of their tissue-selective action, metabolic properties, and oral bioavailability.[2] Like AASs, SARMs act as agonists of the androgen receptor on target tissues such as skeletal muscle and bone. However, in contrast to AASs, SARMS have decreased activity on nontargeted tissues such as the heart, prostate, and liver.[1] Additionally, lack of the 5α-reductase metabolism of SARMs prevents androgenic side effects such as virilization, androgenic alopecia, or prostatic hyperplasia.[2–5] Furthermore, many AASs cannot be delivered orally because of rapid hepatic clearance.[5,6] That has led to the development of 17α-alkylated AASs which reduce hepatic metabolism but increase the risk of liver toxicity.[7] Conversely, SARMs have been developed with good oral bioavailability and are presumed to have reduced hepatotoxicity;[8,9] however, that may not be the case.

To date, no SARM has achieved US Food and Drug Administration (FDA) approval;[10] however, a number of SARMs are currently undergoing clinical trials.[11] Despite the lack of approval, SARMs have made their way into the world of muscle and performance enhancement. They substances are widely and illicitly distributed online where they are sought after for their anabolic properties and favorable side-effect profile.[1,12] With the growing popularity of SARM use, the FDA has issued a warning against recreational use because of health risks including myocardial infarction, stroke, and notably, liver toxicity.[13]

As these substances have gained popularity, cases of drug-induced liver injury (DILI) secondary to illicit SARM use have begun to emerge.[14,15] Little is known regarding the overall risks of these substances or their effects on the liver as no SARM has completed appropriate safety investigations.[11] With these emerging concerns of hepatotoxicity, increased awareness is necessary to promote recognition of SARMs as a potential etiology of DILI. Additionally, further clinical knowledge among healthcare providers would allow them to counsel patients on the risks posed by recreational SARM use.

At this time, knowledge regarding SARM-related DILI is sparse; and to date, there is no specific information regarding SARMs on major hepatotoxicity databases such as LiverTox.[16] In this review, we discuss background information, current knowledge, and limitations in the understanding of hepatotoxicity secondary to SARMs.

Keywords: Drug-induced liver injury; Androgen receptor agonist; Cholestasis; Anabolic steroids.

Abbreviations: SARM, selective androgen receptor modulator; AAS, anabolic androgenic steroid; DILI, drug-induced liver injury; FDA, Food and Drug Administration; ULN, Upper Limit of Normal; NAC, N-acetylcysteine.

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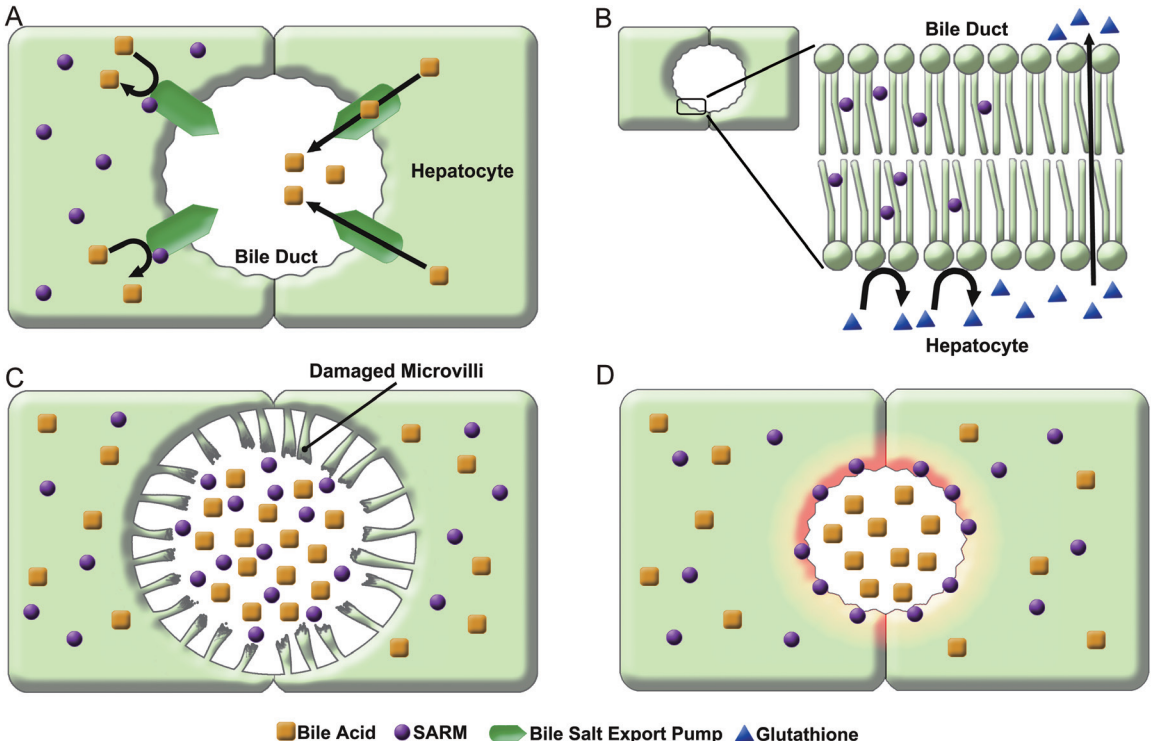

Fig. 1. Proposed mechanisms of bland cholestasis associated with SARMs. (A) SARM binding to bile salt exporter pumps and disrupting bile acid transport from the hepatocyte to the bile duct. (B) SARM molecules interact with the hepatocyte lipid bilayer which decreases the permeability of osmotic factors (e.g. glutathione) that facilitate bile flow. (C) Canalicular microvilli damage seen in hepatocytes metabolizing SARMs with associated biliary stasis and canalicular dilation. (D) SARM induction of hepatocyte and canalicular injury resulting in canalicular contraction and decreased bile flow. SARM, selective androgen receptor modulator.

Methods

A literature review and case-report analysis were conducted utilizing PubMed and Google Scholar by searching for various combinations of terms including, "selective androgen receptor modulator," "SARM," "drug-induced liver injury," "hepatotoxicity," "Ostarine," "enobosarm," "RAD-140," "Testolone," "Ligandrol," and "LGD-4033." The inclusion criteria for case studies were: (1) patients >18 years of age, (2) with elevated liver biomarkers, and (3) SARM use prior to the onset of liver biomarker elevation. The exclusion criteria for case studies were (1) patients with a prior history of liver disease or injury, (2) use of another substance that was more likely to cause a liver biomarker elevation, or (3) an alternate diagnosis was reasonably or more likely to explain liver biomarker elevations. The literature review included basic science studies, clinical trials, and other studies. Current, ongoing, or completed trials involving SARMS were searched on www.clinicaltrials.gov using the previously mentioned search terms, and they were also reviewed.

Hepatotoxicity

While AAS have been sold illicitly for decades, SARMs made their way to the illicit market far more recently, with initial evidence of black-market detection in 2009.[17] Since that time, case reports of DILI have begun to emerge, with the first reported case in 2020.[14] Given the gross similarities between AAS and SARMs, a significant insight into DILI from SARMs can be gained through an understanding of hepatotoxicity from AAS. AAS have been reported to cause four specific forms of DILI, which include direct hepatotoxicity, acute cholestatic syndrome, peliosis hepatis, and liver tumors. These forms of hepatotoxicity have been primarily attributed to 17α-alkylated AAS, and SARMs have been observed to cause a pattern of liver injury that is analogous to this specific subset of steroids.[7,14,18]

17α-alkylated AASs have been modified to be more resistant to liver degradation so that they have decreased first-pass metabolism, allowing for better oral bioavailability and more stable serum levels. However, reduced liver clearance increases the potential for hepatotoxicity.[19] Much like this class of AASs, SARMs have been designed for adequate oral bioavailability with decreased liver degradation which would likely create a similar potential for hepatotoxicity.[8,15]

17α-alkylated AASs induce a characteristic pattern of DILI that manifests as acute cholestatic syndrome, which syndrome is rarely seen with esterified, injectable AASs.[7] In case reports of DILI from SARMs, a similar pattern of acute cholestatic syndrome has been observed. Both 17α-alkylated AASs and SARMs have shown a characteristic bland cholestasis in which there is minimal hepatocellular injury, inflammation, sclerosis, or ductopenia. It manifests as a marked elevation in serum bilirubin and more mild elevations in hepatic enzymes.[20–22]

While hepatotoxicity from SARMs or 17α-alkylated AAS is not understood, there have been numerous suggested mechanisms of acute cholestatic injury from 17α-alkylated AASs that can be extrapolated to SARMs (Fig. 1). One possibility is that the drug binds to canalicular membrane transporters, and accumulation of toxic bile acids induces pump failure impairing bile transport.[23–24] Another postulated mechanism is that the drug decreases the permeability of the biliary epithelium to water and disrupts osmotic factors such as glutathione which then reduces bile flow in the canalicular ducts.[23,25] Additionally, rats that were ad-

ministered 17α-alkylated AASs were noted to have loss of canalicular microvilli potentially leading to biliary stasis and canalicular dilation.[23,26] Furthermore, drug-induced injury of the canalicular, pericanalicular, and basolateral plasma membrane has been noted to induce canalicular contraction.[23,26] Lastly, a genetic defect in the canalicular transport protein may have a contributory role.[23–24] Overall, a complex interplay of these mechanisms could be at work when the injury develops.

Regardless of the mechanism, SARMs and AAS likely share similar pathophysiologic characteristics involving cholestatic injury that is thought to be idiosyncratic in nature. This would be suggested by the rarity of SARM-related DILI relative to the prevalence of SARM use.[2,15] Idiosyncratic injury typically consists of non-predictable hepatotoxicity in specific individuals who are susceptible to injury and is not related to dose. Latency period in idiosyncratic injury can vary as was seen in a number of SARM-related DILI cases in which the time to symptoms onset ranged from approximately 4 to 12 weeks.[27–29]

Outside of the acute cholestatic syndrome, clinical trials have shown that SARMS have the potential to induce transient liver enzyme elevations that have resolved without discontinuation of the drug.[30,31] 17α-alkylated AASs have also been linked to transient serum elevations that resolve without discontinuation.[7] That suggests that both classes of drugs have a similar form of mild, short-lived hepatocellular injury. Anecdotal reports of mild transaminase elevations in users of illicit SARMs have appeared online.[31–35] Given that the serum enzyme elevations are asymptomatic, and that many illicit users are not routinely monitored,[36] the extent of users experiencing these elevations has not been elicited. Considering that liver enzyme elevations from SARMs have been shown to be transient, mild transaminase elevations in recreational SARM users may resolve without intervention or even without discontinuation of the offending SARM.

Other forms of liver injury that have been linked to AAS include vascular changes and tumors. Peliosis hepatis is a syndrome that can occur with prolonged AAS use in which proliferation of sinusoidal hepatic capillaries create blood filled sinusoids and cysts in the liver resulting in an enlarged, red, and fragile liver. Prolonged AAS use has also been linked to nodular regenerative hyperplasia, hepatic adenomas, and hepatocellular carcinoma which are thought to develop due to an unregulated growth stimulus on hepatocytes.[7,19] At this time, no cases of SARMs causing peliosis hepatis, hyperplasia, or tumors in the liver have been reported. However, taking into consideration that SARMs have a similar anabolic potential for growth stimulus on tissues, these manifestations of liver injury are plausible with prolonged, high-dose SARM use.[29,37]

Although these various forms of toxicity have been primarily observed with oral steroids and oral SARMs, the effects have less frequently been observed with intramuscular injections of AAS.[7] While not approved and not studied in any clinical or preclinical trials, injectable SARMs have made their way into the bodybuilding communities and can be purchased online.[38,39] The implications of injectable SARMs on the liver are unclear. Whether or not these SARMs will have decreased incidence of liver toxicity, like that of intramuscular AAS, remains to be seen. At this time, no cases of liver toxicity from injectable SARMs have been reported.

Overview of common SARMs and hepatotoxicity

Ostarine

Ostarine is a SARM that has a number of other designations including MK-2866, enobosarm, S-22, and GTX-024.[40] It was developed by GTx Incorporated and is currently the most well-studied SARM in the industry.[41] Ostarine has been fast-tracked by the FDA program for the treatment of muscle wasting in non-small cell lung cancer and for the treatment of specific subtypes of metastatic breast cancer.[42–43] It has also been evaluated for treatment of stress urinary incontinence.[44] Currently, Ostarine is the closest SARM to reaching approval, with numerous phase II trials, a completed phase III trial, and an ongoing phase III trial set for completion in 2023.[30,45–47] While Ostarine does not have any approved uses or clear safety data, it is still widely used for performance enhancement by athletes.[12] Two cases of DILI have been reported in relation to the drug.[15,18] Early trials have provided limited information with regard to Ostarine and liver toxicity.

Phase II trials and liver injury of Ostarine

In an initial phase II trial, Ostarine doses ranging from 0.1 to 3 mg were given to 24 healthy men and post-menopausal women for 86 days. Ostarine showed dose-dependent increases in lean body mass and physical function. No significant increases in total bilirubin, GGT, or ALP were noted in the study. Transient elevations were noted in eight of the 24 subjects. For seven of the subjects given unspecified doses of Ostarine, the ALT elevations resolved while remaining on the drug, and none of the subjects had clinically significant abnormal elevations in AST or ALT at the end of the study. One of the eight subjects had an ALT elevation that was 4.2 times the upper limit of normal (ULN), which resulted in discontinuation of the drug. The subject had been receiving a 3 mg dose, the ALT level returned to normal after cessation of treatment, and the ALT elevation was not considered a serious adverse event by the investigators.[30]

Ostarine was subsequently studied in a phase II trial of efficacy and safety in patients with cancer. Subjects were given placebo, 1 mg, or 3 mg of the drug for 113 days. Results showed statistically significant improvements in lean body mass with Ostarine, but no clear improvement in physical function based on stair-climb, hand-grip or six-meter walk tests. Three of 54 patients receiving 3 mg of Ostarine had transient ALT elevations that resolved while still on the drug. Only one of those subjects had ALT elevations that were greater than three times the ULN. The investigators reported no clinically significant bilirubin elevation across all treatment groups including placebo, but the data were not shown.[45]

Ostarine was later evaluated for treatment of stress urinary incontinence in post-menopausal women. The study was not published, but GTx Incorporated reported that it failed to show statistically significant improvement in stress urinary incontinence compared with placebo. AST and ALT elevations were noted in one out of 163 subjects in the 1 mg group and one of 163 subjects in the 3 mg group. ALP elevation was noted in only one out of 163 subjects in the 1 mg group and no ALP elevations were reported in the 3 mg group. All the elevations were reported as non-serious adverse events. No AST, ALT, or ALP elevations were noted in the placebo group.[44,48]

While Ostarine was initially evaluated for its anabolic properties, it has since undergone evaluation for androgen receptor targeted therapy of breast cancer. A phase II open-label clinical trial evaluated the efficacy and safety of Ostarine in combination with pembrolizumab for the treatment of androgen receptor-positive, triple-negative metastatic breast cancer. 18 participants were given 200 mg of pembrolizumab every 3 weeks in combination with 18 mg of Ostarine daily. The study was terminated early at 16 weeks

but Ostarine was well tolerated, with three grade 3 adverse events that were not related to the liver. Three participants had grade 1 elevations of AST 1–2.5 times the ULN one had a grade 2 AST elevation of 2.5–5 the ULN. Two participants had grade 1 elevations in ALT and one participant had grade 2 elevations in ALT. The investigators did not report whether the elevations were transient and did not report whether changes of total bilirubin or ALP were monitored.[49]

Another recent phase II open-label clinical study evaluated the correlation between the degree of androgen receptor expression and degree of antitumor activity of Ostarine. The target population consisted of patients with androgen receptor and estrogen receptor-positive metastatic breast cancer. 72 patients were given 9 mg of Ostarine daily and 64 patients were given 18 mg of Ostarine daily for a total of 24 weeks. Greater androgen expression in malignancy was correlated with greater antitumor activity of Ostarine in both the 9 mg and the 18 mg groups. No patients in the 18 mg group had AST elevations. One of 72 patients in the 9 mg group had an elevated AST, which was considered a serious adverse event. The investigators did not specify the degree of elevation or if this elevation was transient. They also did not specify if any other liver function tests were monitored in the study.[47,50]

Phase III trials and liver injury associated with Ostarine

Ostarine was the first SARM to undergo a phase III clinical trial. The POWER1 and POWER2 trials were two identical randomized, double-blind, placebo-controlled studies to evaluate the efficacy of Ostarine for the treatment of muscle wasting in non-small cell lung cancer. Participants were given 3 mg of Ostarine versus placebo. No study results were published; but GTx Incorporated reported that Ostarine failed to meet endpoints for improvement in lean body mass and physical function compared with placebo. The POWER1 trial did not report on liver enzymes in relation to the drug. The POWER2 trial reported increased hepatic enzymes in one of 165 patients receiving 3 mg of Ostarine and no hepatic enzyme changes in the placebo group. The results did not specify which enzymes were elevated or the degree of elevation.[46,50–52]

LGD-4033

LGD-4033, also referred to as Ligandrol or VK5211, is a SARM developed by Ligand Pharmaceuticals and under evaluation by Viking Therapeutics.[53–55] It has been evaluated for use in augmenting hip fracture recovery. As with all SARMS, the drug has not achieved FDA approval and only remains at phase II of clinical trials.[56–58] Although no approved uses or concrete safety data exists, LGD-4033 is widely used in the athletic and fitness communities.[12] Despite emerging cases of liver toxicity in relation to LGD-4033, initial trials have yet to report any evidence of liver toxicity.

Phase I trials and liver injury associated with LGD-4033

In an initial phase I trial, a single increasing dose study was conducted in 48 healthy male volunteers. Subjects were given 0.1–22 mg LGD-4033 to determine its pharmacokinetics and safety profiles. The study reported that LGD-4033 was safe and well tolerated at all tested doses. However, the published report did not specify the duration of LGD-4033 use and failed to comment specifically on liver toxicity.[59] Subsequently, a multiple increasing dose study was conducted on 76 healthy men to determine the effect on lean muscle mass. Subjects were given placebo, 0.1, 0.3, or 1 mg LGD-4033 for 21 days. Lean muscle mass increased in a dose-dependent manner. The reports mentioned that LGD-4033 was safe and well tolerated at all of the tested dosages and specifically mentioned that there were no clinically significant changes in AST or ALT. The report did not specify if other liver function markers were assessed in the study.[60] A third phase I study was conducted to evaluate the tolerability, safety, and pharmacokinetics of LGD-4033 in elderly men and women as that would represent the target hip fracture population. Once again, LGD-4033 was shown to be safe and well tolerated, but the investigators did not specifically comment whether liver function markers were assessed.[61]

Phase II trials and liver injury associated with LGD-4033

To date, one phase II clinical trial has investigated the efficacy LGD-4033 for augmenting the recovery and functional status in patients healing from a hip fracture. It included108 elderly men and women who had suffered a recent hip fracture who were given 0.5, 1, or 2 mg LGD-4033 daily for 12 weeks. Statistically significant and dose-dependent increases in lean body mass and functional performance testing (6 minute walk test) were observed when compared with placebo. LGD-4033 was reported to be safe and well tolerated with no serious adverse events. However, the reports did not mention whether liver function makers had been evaluated.[56,58,62]

RAD-140

RAD-140, also known as Testolone, is a SARM developed by Radius Health Incorporated and licensed to Ellipses Pharmaceuticals.[63–64] It has been evaluated for treatment of hormone receptor-positive breast cancer and neurodegenerative disease.[65,66] Currently, the drug has not achieved FDA approval for use and remains in phase I of clinical trials. Despite lack of approval or clear safety data, RAD-140 remains among the most widely used SARMs for athletic performance.[12] An initial trial for RAD-140 has reported evidence of liver toxicity.

Clinical trials and liver injury associated with RAD-140

A recent phase I dose escalation trial aimed to evaluate the safety, pharmacokinetics, and antitumor activity of RAD-140 in women with androgen receptor-positive/estrogen receptor-positive/ human epidermal growth factor receptor 2 negative metastatic breast cancer. Participants were given 50 mg (6 subjects), 100 mg (13 subjects), or 150 mg (3 subjects) RAD-140 for a median of 8 (range, 1–25) weeks. Preliminary results indicated that RAD-140 had androgen receptor binding and antitumor activity in breast cancer patients.[31,65] The study monitored liver biomarkers when evaluating adverse events. AST elevations were reported in 59% of subjects (23% with grade 3–4), ALT elevations in 45% (23% with grade 3–4), ALP elevations in 14% (5% with grade 3–4), and total bilirubin elevations in 27% (14% with grade 3–4). Grade 3–4 adverse events were catego-

Table 1. Demographics, past medical history, purpose of use, and clinical presentation in cases of SARM-related DILI

SARM	Sex	Age	Purpose of use	PMH	Other drugs	Clinical presentation	Reference
RAD-140	Male	24	-	None	None	Jaundice; Abdominal pain; Pruritus	Yaramada *et al*.[67]
RAD-140	Male	38	-	Daily alcohol use	None	Jaundice; Abdominal pain	Bailey *et al*.[20]
RAD-140	Male	31	Muscle building	Asthma	None	Jaundice; Abdominal pain; Pruritus	Baliss *et al*.[29]
RAD-140	Male	49	-	Depression	Venlafaxine	Jaundice; Pruritus	Flores *et al*.[14]
RAD-140/ LGD-4033	Male	52	Muscle building	Daily alcohol use; Marijuana	None	Jaundice; Abdominal pain; Pruritus; Diarrhea	Barbara *et al*.[21]
LGD-4033	Male	32	Muscle building	None	None	Jaundice; Abdominal pain; Fatigue; Pruritus/ excoriations; Body aches; Nausea; Acholic stool; Malnourished	Barbara *et al*.[28]
LGD-4033	Male	19	Muscle mass	None	None	Jaundice; Dark urine; Light colored stools	Koller *et al*.[15]
LGD-4033	Male	24	-	Binge drinking	None	Jaundice; Anorexia; Weight loss; Nausea; Lethargy	Flores *et al*.[14]
LGD-4033/ Ostarine	Male	28	Bodybuilding	None	Protein supplements; Amino acids; Fat burners	Jaundice; Nausea; Fatigue	Koller *et al*.[15]
Ostarine	Male	40s	Muscle bulk; Weight training	None	Zopiclone; Finasteride	Jaundice; Anorexia; Weight loss; Lethargy; Diarrhea	Bedi *et al*.[18]
Unnamed SARM	Male	29	Bodybuilding	None	Preworkout drinks	Jaundice; Fatigue; Light colored stools; Dark urine	Khan *et al*.[37]
Unnamed SARM	Male	39	-	None	None	Jaundice; Fatigue; Dark urine; Vomiting	Lam *et al*.[68]

SARM, selective androgen receptor modulator; DILI, drug-induced liver injury; PMH, past medical history.

rized as liver markers greater than five times ULN or bilirubin greater than three times ULN. Four subjects with ALT elevations and two with AST elevations had dose-limiting toxicities that were reported to be reversible. No deaths or discontinuations occurred because of drug-related adverse effects. The study found that a large portion of users had elevated liver enzymes, which raises concern that RAD-140 may have androgenic effects on transaminases that have not been fully elucidated.[31,65]

Epidemiology

Of the cases of SARM-related DILI, patients all were men between 19 and 52 years of age (Table 1). The majority were in their 20s and 30s. All cases that reported a reason for use cited bodybuilding or increase of muscle mass as the primary goal of taking the SARM. Most of the men had no medical histories other than alcohol use, marijuana use, or asthma. Aside from bodybuilding supplements, the men were not using other medications except for one who was on venlafaxine and another who was on zopiclone and finasteride.[14,15,18,20,21,28,29,37,67,68]

The demographics of patients with DILI from SARMs were highly consistent with the demographics of DILI from AAS. From 1994 to 2013, all cases of DILI from AAS in the Spanish DILI Registry and Latin DILI Network were in men from 20 to 49 years of age with a mean of 32 years.[69,70] Much like AAS, SARMS use is highly prevalent in young adult men from 18 to 40 years of age who are seeking performance enhancement,[71] so this is expectedly the most typical population where DILI from SARMs was reported.

At this time, no women or geriatric patients have been reported to have developed DILI from SARM use. However, they are specific groups that are targeted in clinical trials and therapeutic applications as SARMs can treat specific diseases such as breast cancer or osteoporosis.[1] Should SARMs become approved for treatment in specific diseases, there remains the concern that those demographics would be susceptible to DILI from SARMs. Furthermore, diseased and older individuals would likely have comorbidities, which leaves the potential for greater morbidity or even mortality compared with DILI in young men. At this time, it remains to be seen how approving the use of SARMs for treatment of various diseases would affect the prevalence of SARM-related DILI.

Clinical presentation

In instances of SARM-related DILI, a primary presenting symptom was jaundice, which was reported in all cases (Table 1). Other symptoms included abdominal pain, nausea, vomiting, diarrhea, fatigue, anorexia, malnourishment, weight loss, body aches, pruritus, dark urine, and acholic

Table 2. Reported liver function markers and INR values upon initial presentation in cases of SARM-related DILI

SARM	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	Total bilirubin (mg/dL)	INR	Reference
RAD-140	71	171	151	–	10.8	0.85	Yaramada *et al*.[67]
RAD-140	55	64	102	–	11.9	1.3	Bailey *et al*.[20]
RAD-140	145*	293*	122*	–	8.4	–	Baliss *et al*.[29]
RAD-140	59	54	327	60	17.0*	1.2	Flores *et al*.[14]
RAD-140/LGD-4033	36	46	529	47	34.5	1.0	Barbara *et al*.[21]
LGD-4033	33	45	425	–	35.0	1.1	Barbara *et al*.[28]
LGD-4033	–	132*	92.4*	24.6*	13.9*	0.98	Koller *et al*.[15]
LGD-4033	111	273	289	62	6.8*	1.0	Flores *et al*.[14]
LGD-4033/Ostarine	–	145*	92*	–	23.5*	1.07	Koller *et al*.[15]
Ostarine	69	112	268	49	19.9*	1.3	Bedi *et al*.[18]
Unnamed SARM	79	165	213	–	16.9	–	Khan *et al*.[37]
Unnamed SARM	48	92	105	–	12.4	0.9	Lam *et al*.[68]

Reference ranges: ALT 7–55 U/L, AST 9–48 U/L, total bilirubin 0.1–1.2 mg/dL, ALP 40–129 U/L, GGT 8–61 U/L. *Unit of measurement was converted to SI units from reported value in case. SARM, selective androgen receptor modulator; DILI, drug-induced liver injury; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, international normalized ratio.

stools. Virtually all symptoms were constitutional or gastrointestinal. There were no other pathologic findings involving other organ systems.[14,15,18,20,21,28,29,37,67,68] These specific symptoms were highly consistent with bland cholestasis, in which there is an insidious onset of jaundice and pruritus.[22]

Lab findings

Hepatic function testing upon initial presentation in SARMs-related DILI has shown fairly consistent patterns across the majority of cases (Table 2). AST elevations were all within three times the ULN, with the exception of one patient who was only slightly above that cutoff. ALT elevations were all less than or equal to three times the ULN with the exception of two patients who were moderately above this cutoff. There was some degree of variation with ALP elevations in which seven patients had ALP elevations that were less than two times the ULN. However, an additional five patients had ALP values between two and five times the ULN. All of the cases had marked bilirubin elevations that were 2.5 times the ULN. No elevations of GGT values were reported. INR values were either normal or mildly elevated in all reported cases.[14,15,18,20,21,28,29,37,67,68] The findings are in line with the pattern of hepatic function markers noted in bland cholestasis. In bland cholestasis, ALT values are typically < 200 U/L or less than five times the ULN. Bilirubin is typically greater than 2.5 times the ULN. The findings were seen in virtually all cases except for one that had a slightly higher ALT, but higher elevation of ALT within five to 10 times ULN can be seen early in the clinical course of bland cholestasis.[22]

ALP findings in bland cholestasis are typically less than two times the ULN despite a normal GGT.[22] The majority of cases were consistent with this pattern, although five reported cases did have ALP elevations that exceeded the cutoff. Four of the cases that reported significant ALP elevations reported normal GGT values, which suggests that the ALP elevations may have been caused by other metabolic processes such as increased bone turnover. Overall, with the exception of potentially higher ALP elevations, hepatic function markers in SARM-related DILI appear to be consistent with those in bland cholestasis.

Radiologic findings

Cases of SARM-related DILI involved various forms of hepatobiliary imaging including ultrasound, CT, and MRI. As expected in bland cholestasis, no clear evidence of intrahepatic or extrahepatic biliary obstruction was reported on imaging in any case (Supplementary Table 1). One case reported intrahepatic biliary dilation in one patient, however a CT scan of the same patient reported no intrahepatic dilations. The only significant finding was hepatomegaly in three of 12 of the cases, one of who was also noted to have associated splenomegaly. There were no cases of hepatic tumors or peliosis hepatis in any of the cases, although one did report a small hepatic cyst. For the most part, radiologic findings in these cases of DILI appeared to be nonspecific and primarily served to rule out other causes of liver injury.[14,15,18,20,21,28,29,37,67,68]

Histologic manifestations

Histologic manifestations seen in acute cholestatic syndrome from SARMs present analogously to that of 17α-alkylated steroids. In cholestatic injury from AAS, a distinctive bland cholestasis is seen with minimal hepatocyte necrosis or inflammation. There was little duct injury or ductopenia, however canalicular dilatation and bile plugs were seen.[23,72–73] This pattern of injury was rarely seen aside from estrogen-associated cholestasis or intrahepatic cholestasis of pregnancy.[22]

With the rise in cases of DILI from SARMs, a similar pattern of injury has been observed. Of the 12 reported cases of SARMs that were reviewed, 10 reported liver biopsies (Table 3). All of the biopsies had some form of cholestasis with the majority reporting either bland or canalicular cholestasis. All cases with inflammation, fibrosis, duct damage, or ductopenia reported mild, minimal, or sparse findings. This pathology was highly consistent with the bland cholestasis that was specific to AAS induced liver injury which suggests that SARMs have the potential to induce highly comparable histopathologic effects on the liver.[14,15,18,20,21,28,37,67,68]

Table 3. Reported biopsy findings in cases of SARM-related DILI

SARM	Histologic Findings	Reference
RAD-140	Blank canalicular cholestasis without inflammation	Yaramada *et al*.[67]
RAD-140	Bland cholestasis	Bailey *et al*.[20]
RAD-140	Moderate cholestasis; Ductopenia; Minimal fibrosis and inflammation	Flores *et al*.[14]
RAD-140/ LGD-4033	Diffuse centrilobular canalicular cholestasis; Prominent ductular reaction; Mild lobular inflammation with rare non-necrotizing epithelioid granuloma; Mild portal and periportal fibrosis; Mild to moderate hemosiderosis	Barbara *et al*.[21]
LGD-4033	Cholestatic hepatitis; Mild portal, periportal, and perisinusoidal fibrosis	Barbara *et al*.[28]
LGD-4033	Mild septal fibrosis; Canalicular cholestasis in hepatocytes with biliary plugs; Ductopenia and loss of bile ducts in ductal spaces	Koller *et al*.[15]
LGD-4033/ Ostarine	Mild bridging fibrosis; Centrilobular canalicular cholestasis; Destruction of bile ducts with bile plugs	Koller *et al*.[15]
Ostarine	Mild ductular reaction with mild duct damage and minimal inflammation; Moderate to severe centrilobular cholestasis with sparse portal inflammation	Bedi *et al*.[18]
Unnamed SARM	Bile Stasis with lipofuscin pigment; Collection of neutrophils (micro-abscesses) within the lobular parenchyma; Centrilobular intracytoplasmic bile pigment; Portal tracts with sparse inflammatory cells	Khan *et al*.[37]
Unnamed SARM	Cholestatic injury; Normal hepatic architecture	Lam *et al*.[68]

SARM, selective androgen receptor modulator; DILI, drug-induced liver injury.

Treatment and outcomes

In all twelve reported cases of DILI, patients were reported to have stopped the offending SARMs. A number of cases took no further intervention aside from supportive care while several others intervened with N-acetylcysteine (NAC) or ursodiol. Four cases attempted intervention with ursodiol, and two of those added NAC. One case that used NAC and ursodiol also added silymarin as part of the treatment regimen. Two cases used cholestyramine for symptomatic treatment of pruritus. None of the cases attempted treatment with corticosteroids. Regardless of intervention or supportive measures, all participants showed improvement in their liver function tests within months. No fatalities or liver transplants were reported in any of the 12 cases. No cases were rechallenged with the offending SARM.[14,15,18,20,21,28,29,37,67,68] The outcomes are consistent with recovery that has been observed in acute cholestatic syndrome from 17α-alkylated AAS, in which patients typically make a full recovery after stopping the offending agent.[7,74] Ursodiol is often used, but its efficacy has not been clearly established.[75] The role of N-acetylcysteine in treating DILI outside of acetaminophen induced injury has not been clearly established, but it has been used to treat hepatotoxicity from AAS.[76] Silymarin has been shown to have hepatoprotective effects from AAS induced liver injury in animal models but no clear data in humans exists.[77]

Given that treatment options for acute cholestatic syndrome from AAS are not well established, finding an appropriate treatment strategy for acute cholestatic syndrome from SARMs would likely present a challenge. As with many causes of DILI, the first priority would be to stop the offending SARM. Considering that the drugs are used illicitly for bodybuilding or athletic performance, patients may be reluctant to stop SARM use. At this time, it is not clear whether decreasing the dose or trialing a different SARM would cause a similar injury. However, given the risk of harm, it would be prudent to discourage future use of any SARM or AAS in these patients. Other treatments such as NAC or ursodiol can be attempted, particularly if recovery is prolonged, as they have a low risk of harm.[78] Regardless of intervention or supportive care, if patients cease further SARM use, hepatic recovery can likely be expected over the course of months.

Concomitant substance use

Regarding SARM use causing DILI, one confounding factor during patient presentations is the use of concomitant substances along with SARMs. The most common reason for SARMs use is improved performance or muscle enhancement, and patients may be concurrently using multiple substances including AAS, other hormones, or various supplements. Additionally, illicit SARMs may be contaminated, laced, or doped with other substances. One analysis found that only 52% of SARMs purchased online actually contained SARMs and 39% contained other unapproved drugs.[10] Two of the cases of SARM-related DILI reported that the SARMs were sent for toxicologic analysis and the specified SARMs were confirmed without other contaminants.[14] Furthermore, users of performance enhancing drugs are known to undergo a post-cycle therapy in which they take specific drugs such as aromatase inhibitors or estrogen receptor antagonists. The goal of these drugs is to minimize hypogonadal effects or muscle loss after completing a cycle of SARMs.[12,15] Overall, the use of multiple substances may make DILI from SARMs difficult to identify or confirm as the primary driver of hepatotoxicity. However, the presentation of an acute cholestatic syndrome or bland cholestasis should raise clinical suspicion for SARMs as a potential culprit.

Conclusions

SARMs use is widespread among young men seeking to enhance athletic performance, and cases of DILI secondary to these drugs are emerging. As illicit use expands or SARMs gain approval for use, increasing cases of SARM-related DILI are likely to emerge. Given the novelty of this class of drugs, clinical knowledge and understanding in cases of SARM-related DILI is sparse. However, based on evidence

from a number of cases, the drugs manifest a form of hepatotoxicity that is similar to the bland cholestasis that can be precipitated by oral AASs. Diagnosis would likely involve ruling out other causes of liver injury and confirming laboratory or biopsy findings consistent with bland cholestasis. Apart from cessation of the drug, no clear treatments exist for SARM-related DILI, however prognosis and recovery are favorable with supportive treatment. Ultimately, further study is required to understand the diagnosis, treatment, outcomes, and complications of SARM-related DILI.

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Conflict of interest

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Author contributions

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