Drug-Induced Liver Injury by Selective Androgenic Receptor Modulators

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Selective androgenic receptor modulators (SARMs) have not been approved by the U.S. Food and Drug Administration but they are heavily promoted as alternatives to androgenic anabolic steroids. We present two cases of liver injury associated with SARMs. (*Hepatology Communications* 2020;4:450-452).

Traditional androgenic anabolic steroids (AASs), like testosterone, have positive anabolic (bone, muscle) actions, but androgenic (virilization, acne) effects limit their use. Selective androgenic receptor modulators (SARMs), such as Ligandrol, enobosarm, and RAD-140, bind androgen receptors with tissue-selective activity that promotes anabolic actions without significant androgenic effects. Although not U.S. Food and Drug Administration approved, they are heavily promoted as AAS alternatives and are being trialed in aging and muscle-wasting disorders. Unlike AASs, which have well-recognized hepatotoxic potential, only limited human hepatic safety data are available for SARMs.[1-4]

Patients and Methods

CASE 1

A previously healthy 24-year-old man presented with a 5-week history of jaundice, anorexia, nausea, lethargy, and weight loss of 5 kg. He had used a gym supplement (LGD-4033 LIGANDROL capsules) for 9 weeks, and his symptoms developed a week after its cessation. He had a history of binge drinking once a month. He was not on any regular medications and gave no previous history of liver disease.

Examination revealed normal vital signs, jaundice, and mild hepatomegaly, without peripheral stigmata of chronic liver disease. His liver tests showed the following: bilirubin, 116 μmol/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); gamma-glutamyl transpeptidase (GGT), 62 U/L (reference <110); platelets, 387 × 10^9/L (reference, 150-450); international normalized ratio (INR), 1.0; globulin, 34 g/L; creatinine, 114 (reference, <110 μmol/L); eosinophil count, 0.21 × 10^9/L (reference, 0.00-0.70); and R ratio of 8.22 (indicating hepatocellular liver injury). Viral, autoimmune and metabolic liver diseases, and biliary obstruction were excluded by blood tests and liver ultrasonography.

The subject's bilirubin peaked at 116 μmol/L after 2 weeks, but his liver tests and creatinine normalized over 4 months (Table 1). Rechallenge was not performed.

CASE 2

A 49-year-old man presented with jaundice and itching of 5 weeks duration. His only regular medication was an antidepressant (venlafaxine) for 11 months. Four months prior to presentation, he reported using a SARM (RAD-140) for 4 weeks and intermittent use thereafter. Investigations showed the following: bilirubin, 291 umol/L; ALT, 54 U/L; AST, 59 U/L; ALP, 327 U/L; GGT, 60 U/L; albumin, 40 g/L; globulin, 28 g/L; creatinine, 120 μmol/L (peaking at 132 μmol/L); INR, 1.2;

Abbreviations: AAS, androgenic anabolic steroid; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; SARM, selective adrenergic receptor modulator.

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TABLE 1. TREND OF AVAILABLE LIVER TESTS RELATED TO NONSTEROIDAL SARM USE FOR CASE 1

Case 1

Timeline	ALT, U/L (<40)	AST, U/L (<40)	ALP, U/L (30-110)	Bilirubin, μmol/L (2-20)	Comment
Baseline	29	—	111	4	4 years prior
–6 weeks					SARM use ceased after 9 weeks of use
–2 weeks	589	175	197	68	Symptoms present for 3 weeks when seen by primary care physician
–1 week	273	111	289	116	Referred to hepatologist
Initial review by hepatologist	160	76	272	92	
2 weeks	334	155	266	46	
4 weeks	178	—	182	23	
8 weeks	79	—	134	18	
8 months	20	—	96	13	

platelets, 347 × 10^9/L; and R ratio of 5.0 (indicating mixed hepatocellular–cholestatic liver injury). Alcohol consumption was insignificant. Appropriate blood tests and liver imaging excluded other liver diseases and biliary obstruction. Liver histology showed moderate cholestasis with ductopenia and minimal fibrosis and inflammation, consistent with drug-induced liver injury. Venlafaxine was ceased, and he was treated with ursodiol and cholestyramine. His bilirubin peaked at 346 μmol/L but gradually improved over 2 months; all his liver tests and creatinine were completely normal when rechecked 12 months after his initial presentation (Table 2). Rechallenge was not performed.

Results

In both cases, the supplements were sent for toxicologic analysis and were screened by ultra-high performance liquid chromatography/photodiode array and gas chromatography–mass spectrometry. The presence of SARM in both cases (Ligandrol in case 1 and RAD-140 in case 2) was confirmed, and no other contaminants were identified.

Discussion

To our knowledge, these individuals represent the first cases of significant liver injury with SARM. Mild, transient, self-limiting increases in aminotransferases were reported in clinical trials,[1-4] but discontinuation due to raised ALT was rare (one case), and serious liver injury was not documented. Causality assessment scores (Roussel Uclaf Causality Assessment Method) for cases 1 and 2 were 7 and 6 points (probable), respectively.[5] The Drug Induced Liver Injury Network (DILIN) causality score was

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TABLE 2. TREND OF AVAILABLE LIVER TESTS RELATED TO NONSTEROIDAL SARM USE FOR CASE 2

Case 2

Time line	ALT, U/L (<40)	AST, U/L (<40)	ALP, U/L (30-110)	Bilirubin, μmol/L (2-20)	Comment
Baseline	24	21	57	10	8 months prior
–2 weeks	200	111	111	80	Ordered by primary care physician for pruritus; referred to hepatologist; SARM use had ceased after intermittent use for months
Initial review by hepatologist	54	63	327	291	
2 weeks	51	—	299	321	
3 weeks	44	61	286	346	
4 weeks	60	65	262	187	
8 weeks	172	123	121	32	
12 months	27	—	59	7	

2 (probable) for both cases, and the DILIN severity score was 2 (moderate liver injury, case 1) and 3 (moderate to severe liver injury, case 2).[6] In both cases, the presence of SARM in the supplements was confirmed and other contaminants (especially AASs) were excluded. In the first case, alcohol was a potential confounding factor, but the pattern of liver tests (ALT>AST, normal GGT) was inconsistent with alcoholic hepatitis. In the second case, it is possible that venlafaxine may have contributed; however, he had been taking this for nearly a year, whereas venlafaxine hepatotoxicity is usually seen within 1 to 3 months (https://livertox.nih.gov).

The liver injury in both cases is within the described spectrum of liver injury associated with AASs. While case 2 showed the more well-known cholestatic injury profile, the hepatocellular presentation of case 1 is also well described. These off-target effects question the so-called tissue selectivity of SARMs, which has been their main selling point.

Whether these cases represent the "tip of the iceberg" remains to be seen, but given the increasing popularity of SARM use, greater vigilance and reporting of potential cases is required.

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