RAD-140 Drug-Induced Liver Injury

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Background: RAD-140, one of the novel selective androgen receptor modulators (SARMs), has potent anabolic effects on bones and muscles with little androgenic effect. Despite the lack of approval for its clinical use, RAD-140 is readily accessible on the consumer market. Hepatotoxicity associated with the use of SARMs has only rarely been reported in the literature.

Case Report: A 24-year-old male presented with a 2-week history of diffuse abdominal pain, scleral icterus, pruritus, and jaundice. Prior to presentation, he had been taking the health supplement RAD-140 for muscle growth for 5 weeks. He had a cholestatic pattern of liver injury, with a peak total bilirubin of 38.5 mg/dL. Liver biopsy was supportive of a diagnosis of RAD-140-associated liver injury characterized pathologically by intracytoplasmic and canalicular cholestasis with minimal portal inflammation. Symptoms and liver injury resolved after cessation of the offending agent.

Conclusion: To date, only select descriptions of the potential hepatotoxicity associated with the use of SARMs, including RAD-140, have been published. Given their potential hepatotoxicity and ready availability on the consumer market, RAD-140 and other SARMs should be used judiciously and under close clinical supervision until further hepatic safety data become available.

Keywords: Chemical and drug induced liver injury, Enobosarm, LGD-4033, RAD140

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INTRODUCTION
Nonsteroidal selective androgen receptor modulators (SARMs), including RAD-140, Enobosarm, and Ligandrol, promote anabolic effects on bones and muscles through binding to androgen receptors, similar to traditional anabolic-androgenic steroids such as testosterone.1-3 Unlike anabolic-androgenic steroids, SARMs do not have the unwanted androgenic effects because they are not metabolized to dihydrotestosterone by 5-alpha reductase or to estrogen by aromatase.2 Because of the high tissue selectivity of their anabolic actions, SARMs are being studied in several clinical applications, including sarcopenia, cancer-related cachexia, prostate cancer, breast cancer, and osteoporosis.1 Despite receiving a warning from the US Food and Drug Administration and being banned by the World Anti-Doping Agency, SARMs remain readily accessible in the online marketplace and are used as alternatives to anabolic-androgenic steroids for muscle and strength development.4-6 Unlike anabolic-androgenic steroids, which have a well-known hepatotoxic profile, only limited hepatic safety data are available for SARMs.3,7-12 We report a case of drug-induced liver injury caused by the use of the SARM RAD-140.

CASE REPORT
A previously healthy 24-year-old male presented to the emergency department (ED) with a 2-week history of diffuse abdominal pain, pruritus, scleral icterus, and jaundice. Approximately 2 months earlier, he had started taking up to 15 mg daily of RAD-140 for muscle growth. The only other medication that he took was acetaminophen 250 mg/ aspirin 250 mg/caffeine 65 mg (used 4 times daily as needed for headache, no more than twice a week). He had stopped both medications 2 weeks prior to presentation as instructed by his primary care provider (PCP) because of the incidentally finding of elevated liver chemistries (Table 1, Routine PCP office visit, +5 weeks).

In the ED, the patient denied consuming alcohol or using any other supplements, over-the-counter or prescription medications, or recreational drugs. Physical examination was normal except for jaundice and scleral icterus. Laboratory data revealed total bilirubin of 10.8 mg/dL (reference range, 0.2-1.2 mg/dL), alkaline phosphatase of 151 IU/L (reference range, 32-91 IU/L), alanine aminotransferase of 171 IU/L (reference range, 17-63 IU/L), and aspartate aminotransferase of 71 IU/L (reference range, 15-41 IU/L). Gamma-glutamyl transpeptidase, international normalized ratio (INR), total protein, albumin, and complete blood count were within normal limits (Table 1, Emergency department encounter, +7 weeks). Hospital admission for further testing was recommended; however, the patient declined and left against medical advice.

A week after his index hospital encounter, the patient was seen in the hepatology clinic for follow-up, where he was...
Table 1. Liver Test Results

| Timeline                                    | Total Bilirubin, mg/dL (Reference, 0.2-1.2) | ALT, IU/L (Reference, 17-63) | AST, IU/L (Reference, 15-41) | ALP, IU/L (Reference, 32-91) | Platelet Count, x 10^12/L (Reference, 150-450) | INR (Reference, <1.0) | Albumin, gm/dL (Reference, 3.5-4.8) |
|--------------------------------------------|---------------------------------------------|-----------------------------|-----------------------------|----------------------------|---------------------------------|---------------------|---------------------------------|
| Prior to RAD-140 use, -14 months           | 1.0                                         | 48                           | 26                          | 82                         | 152                             | -                   | 4.6                             |
| Started RAD-140                            | -                                           | -                           | -                           | -                          | -                               | -                   | -                              |
| Routine PCP office visit, +5 weeks         | 1.2                                         | 313                          | 182                         | 103                        | 180                             | 0.8                 | 4.4                             |
| Emergency department encounter, +7 weeks   | 10.8                                        | 171                          | 71                           | 151                        | 263                             | 0.85                | 4.1                             |
| Hepatology office visit, +8 weeks          | 32.3                                        | 125                          | 82                           | 181                        | 305                             | 0.96                | 3.9                             |
| Hepatology office visit, +10 weeks         | 24.8                                        | 212                          | 120                          | 251                        | 310                             | 1.47                | 3.0                             |
| Hospital day 1, +10 weeks, 2 days          | 28.7                                        | 155                          | 94                           | 232                        | 341                             | 1.36                | 2.9                             |
| Hospital day 2                             | 26.1                                        | 134                          | 76                           | 203                        | 312                             | 1.46                | 2.5                             |
| Hospital day 3                             | 27.3                                        | 115                          | 62                           | 199                        | 260                             | 1.61                | 2.6                             |
| Hospital day 4                             | 24.3                                        | 117                          | 79                           | 194                        | 268                             | 1.69                | 2.5                             |
| Postdischarge hepatology office visit, +11 weeks | 38.5                                        | 143                          | 104                          | 189                        | 299                             | 0.84                | 2.9                             |
| Postdischarge hepatology office visit, +14 weeks | 24.6                                        | 120                          | 118                          | 187                        | 261                             | 0.89                | 2.9                             |
| Postdischarge hepatology office visit, +18 weeks | 4.9                                         | 118                          | 79                           | 118                        | 170                             | 0.91                | 4.0                             |

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio; PCP, primary care provider.

DISCUSSION

This case of RAD-140–associated cholestatic liver injury had an assessed Drug-Induced Liver Injury Network causal-ity score of 1 (probable) and a severity score of 3 (severe injury). To our knowledge, ours is the sixth case of SARM-associated drug-induced liver injury and the third case associated with RAD-140 use (Table 2). Similar to the

Other

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Table 2. Summary of Cases of Selective Androgen Receptor Modulator (SARM)-Associated Hepatotoxicity

| Study                  | SARM     | Presenting Symptoms                                      | Duration of SARM Use | Initial / Peak Bilirubin, mg/dL | Time to Peak Bilirubin After SARM Cessation | Initial ALT / AST / ALP, IU/L | Initial Platelet Count, $\times 10^9$/L | INR | Liver Histology                                                                 | Management                                      |
|------------------------|----------|----------------------------------------------------------|----------------------|---------------------------------|--------------------------------------------|-------------------------------|---------------------------------|------|---------------------------------------------------------------------------------|------------------------------------------------|
| Flores et al, 2020      | Ligandrol| Jaundice, anorexia, nausea, lethargy, weight loss        | 9 weeks              | 6.78/6.78                       | 5 weeks                                    | 273/111/289                   | 387                             | 1    | --                                                                              | SARM cessation, supportive care                |
| Barbara et al, 2020     | Ligandrol| Jaundice, fatigue, pruritus, weight loss                 | 2 weeks              | 35/38.2                         | --                                         | 229/91/88                     | --                              | 1.1  | Cholestatic hepatitis with mild portal, periportal, and perisinusoidal fibrosis | SARM cessation, supportive care                |
| Bedi et al, 2021        | Enobosarm| Jaundice, anorexia, weight loss, lethargy, diarrhea      | 2 months             | 19.9/43.0                       | --                                         | 112/69/268                    | 313                             | 1.3  | Moderate to severe cholestasis, very mild ductal damage                          | SARM cessation, supportive care                |
| Flores et al, 2020      | RAD-140  | Jaundice, pruritus                                       | 4 weeks and intermittent use thereafter | 17/20.2                          | --                                         | 44/61/286                     | 347                             | 1.2  | Moderate cholestasis, ductopenia, minimal fibrosis and inflammation             | SARM cessation, supportive care                |
| Barbara et al, 2020     | RAD-140 / Ligandrol | Jaundice, right upper quadrant pain, pruritus, diarrhea | 7 weeks              | 34.5/34.5                       | --                                         | 46/36/529                     | --                              | 1.0  | Diffuse canalicular cholestasis, ductal reaction, mild lobular inflammation with rare non-necrotizing epithelioid granuloma and mild portal and periportal fibrosis | SARM cessation, supportive care                |
| Present case, 2022      | RAD-140  | Jaundice, abdominal pain, scleral icterus, pruritus      | 5 weeks              | 1.2/38.5                        | 5 weeks, 6 days                            | 313/182/103                   | 180                             | 0.8  | Moderate intracytoplasmic and canalicular cholestasis, minimal portal inflammation | SARM cessation, supportive care                |

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, international normalized ratio.
Figure. (A) Axial contrast-enhanced computed tomography image shows hepatomegaly and focal fatty infiltration (arrow). (B) Magnetic resonance cholangiopancreatography demonstrates patent biliary tree. (C) Liver histology illustrates hepatocellular and canalicular cholestasis (arrows) (hematoxylin and eosin [H&E] stain, magnification ×40). (D) Liver histology reveals minimal portal inflammation (arrow) (H&E stain, magnification ×20).

previously reported cases, jaundice was the presenting symptom in our patient. Except for one case, SARM-related liver injury was either of mixed or cholestatic pattern.9-12 In our case, we observed a primarily cholestatic pattern of injury, with an initial moderate elevation in transaminases, followed by profound hyperbilirubinemia. We observed a latency period of approximately 6 weeks from cessation of the SARM to peak bilirubin levels, compared to Flores et al who reported a latency period of 5 weeks.9 Similar to Flores et al and Bedi et al, we observed a mild elevation in INR without fulminant liver failure.9,12 Liver biopsies typically demonstrate intracytoplasmic or canalicular cholestasis with minimal or nonexistent necrosis or inflammation. In all cases of SARM-related hepatotoxicity to date, including ours, liver injury resolved with cessation of the offending agent. No patients developed fulminant liver failure, and no deaths occurred. While our patient did not receive any specific treatment for his liver injury, ursodeoxycholic acid may be beneficial in relieving cholestasis related to drug-induced liver injury, although data are largely lacking.13

Our patient had a history of using acetaminophen and salicylic acid prior to the onset of his liver injury. However, acetaminophen and/or salicylic acid–related hepatotoxicity was deemed unlikely because of the small accumulated dosage, and more importantly, the lack of classic zone 3 necrosis/apoptosis and/or microvesicular steatosis. On the other hand, bland cholestasis, a pathologic feature commonly observed in anabolic-androgenic steroid–induced hepatotoxicity, highly suggests cholestatic injury from RAD-140.14

The molecular mechanisms underlying SARM-induced hepatotoxicity are largely speculative. The bland cholestasis seen in both anabolic-androgenic steroid– and RAD-140/Enobosarm–associated hepatotoxicity highly suggests involvement of androgen receptors in dysregulation of bile transport. In animal studies, the bile salt export
pump (BSEP), an ATP-binding cassette subfamily B member 11 (ABCB11) transporter, was reported to be involved in anabolic-androgenic steroid–induced cholestatic injury.\textsuperscript{7,15,16} Whether the association of RAD-140 with androgen receptors regulates BSEP through receptor-associated signaling pathways remains to be defined. In humans, the ABCB11 mutation was reported to increase the genetic susceptibility of anabolic-androgenic steroid–induced cholestasis.\textsuperscript{17} Although we do not know if our patient has the ABCB11 mutation, he is heterozygous for alpha-1-antitrypsin Z (Pi*MZ), a phenotype reported to be a predisposing factor for liver disease and fibrosis.\textsuperscript{18} Whether Z heterozygosity contributes to drug-induced cholestasis remains to be determined.

**CONCLUSION**

The accumulating cases of drug-induced liver injury from SARMs raise concern about their hepatic safety and question the tissue selectivity of these agents. We caution the use of SARMs outside of clinical investigation and advocate for tighter regulation, close monitoring, and prompt reporting of adverse events associated with SARMs.

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