MEDICINAL MISHAP

# Severe liver injury following use of RAD-140, a selective androgen receptor modulator, for body building

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## Case

A 43-year-old Caucasian male presented to his general practitioner (GP) with 2 weeks of jaundice, scleral icterus and pruritis, without abdominal pain or fevers. He had no past history of chronic hepatitis or other liver disease, was not on regular, over-the-counter or as-required medication, and had not used paracetamol recently. There was no known family history of hepatic, connective-tissue or autoimmune disease. He was a nonsmoker, and did not drink alcohol or use recreational drugs.

On examination at his initial presentation, he was alert and oriented, and his observations were within the normal range. He had obvious scleral icterus and jaundice, but no tattoos or needle marks, and no hepatic flap. His abdomen was soft and non-tender with no hepatomegaly or splenomegaly detected.

The blood investigations on his initial presentation showed hyperbilirubinaemia, with a total serum bilirubin concentration of 262 micromol/L. Other liver biochemistry results were unavailable.

He was referred to a private hepatologist, who monitored him in an outpatient setting; however, a deterioration in his blood tests over the next 6 weeks necessitated admission to a tertiary referral hospital. His liver biochemistry at the time of hospital admission suggested acute liver injury, with a total serum bilirubin concentration of 708 micromol/L, and a mixed (cholestatic and hepatotoxic) picture (Table 1). A screen for autoimmune liver disease and viral hepatitis (including hepatitis A, B, C, D, cytomegalovirus and Epstein Barr virus) was negative.

Upon further history taken by the hepatology team, the patient revealed he had been using a selective androgen receptor modulator (SARM) as a body-building supplement. The SARM he reported using was RAD-140 (also known as testolone or radarine). He had procured RAD-140 online, used it for 2 months, but stopped it 1 week before his initial presentation to the GP. He reported no use of other dietary, nutritional or herbal supplements.

**Table 1 Pathology test results on admission to hospital**

| Pathology test | Result | Reference range [NB1] |
|---|---|---|
| **liver biochemistry** | | |
| total serum bilirubin concentration | 708 micromol/L | less than 20 micromol/L |
| serum albumin concentration | 32 g/L | 32 to 45 g/L |
| serum alanine aminotransferase concentration | 158 U/L | less than 35 U/L |
| serum aspartate aminotransferase concentration | 90 U/L | less than 40 U/L |
| serum gamma-glutamyl transferase concentration | 62 U/L | less than 50 U/L (male) |
| serum alkaline phosphatase concentration | 150 U/L | 30 to 110 U/L (male older than 22 years) |
| **other relevant tests** | | |
| INR | 1.5 | less than 1.1 |
| random blood glucose | 5.2 mmol/L | 3.0 to 7.7 mmol/L |
| serum lipase concentration | 36 U/L | less than 140 U/L |

g/L = grams per Litre; U/L = Units per Litre

NB1: Normal ranges are taken from The Royal College of Pathologists of Australia (RCPA) Manual of use and interpretation of pathology tests (Accessed 10 Aug 2023), except for INR and lipase concentration, which are taken from the patient's laboratory reports.


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The Naranjo questionnaire[1] (designed to determine the likelihood that an adverse reaction was caused by a drug) returned a score of 8, which indicated his acute liver injury was a *probable* adverse drug reaction.

Magnetic resonance cholangiopancreatography was reported as normal. A liver biopsy showed cholestatic hepatitis, bile plugs within the canaliculi, mild focal lobular inflammation, no ductopenia, no cell necrosis and no interface hepatitis. The overall picture was consistent with bland cholestasis, which is common in anabolic steroid–induced jaundice.

Five months after discontinuation of RAD-140 and close monitoring of the bland cholestasis, the patient's total serum bilirubin concentration and other liver biochemistry returned to within reference ranges (Figure 1). The case was reported as an adverse drug reaction to the Therapeutic Goods Administration (TGA).

## Comment

SARMs are not approved by the TGA, yet are readily accessible online as body-building or nutritional supplements. Reports of serious adverse events, particularly hepatotoxicity, have been associated with use of SARMs.[2-4] Due to the variable potencies and toxic effects of these supplements, development of acute liver failure requiring liver transplant is a possibility. This highlights the risks associated with nonmedical supplement use.[2-5]

Despite stopping RAD-140 prior to seeing his GP, this patient's liver biochemistry significantly worsened over the next 6 weeks. Had he continued using it, his acute liver failure may have progressed necessitating orthotopic liver transplantation. Concerningly, he never reported using the SARM to his GP.

Traditional anabolic androgenic steroids, such as testosterone, exert anabolic effects on bone and muscle, and androgenic adverse effects including virilisation, impaired fertility and acne.[6] SARMs, such as RAD-140, ligandrol and enobosarm, activate androgen receptors in muscles and bones and have antagonistic effects on the prostate and seminal vesicles.[2,6]

While SARMs are not approved by the TGA, they are being investigated as potential treatments for muscle wasting (sarcopenia) and bone demineralisation associated with ageing and chronic diseases. They may have a role in improving functional limitation associated with sarcopenia and frailty in older people.[6]

Anabolic steroids are known to have hepatotoxic potential;[6] however, few human studies on hepatic safety of SARMs are available. The mechanism of SARM-associated hepatotoxicity remains elusive, but is thought to be similar to anabolic steroid–associated hepatotoxicity, most likely an idiosyncratic reaction (potentially immune mediated).[3,4]

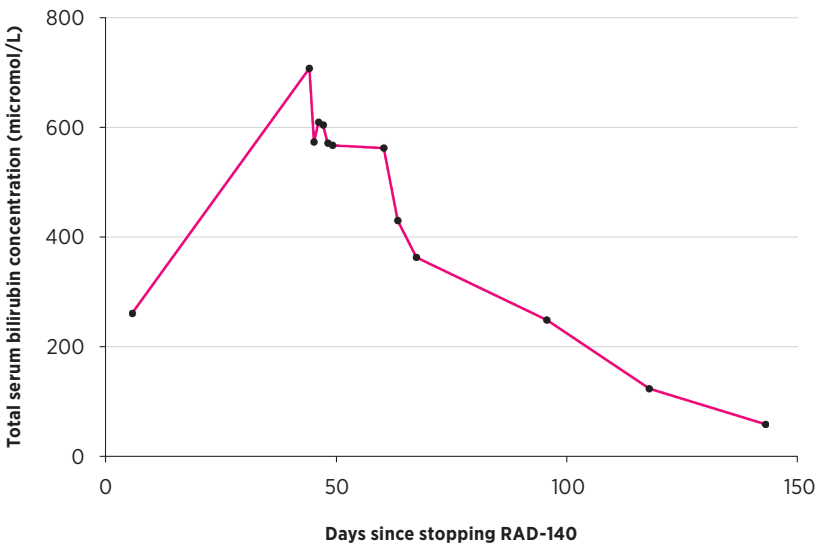
*In vitro* studies of anabolic steroids have shown a toxic increase in bile-acid concentration within hepatocytes due to increased expression of the cytochrome P450 enzyme, CYP8B1.[3] The metabolites of SARMs may also contribute to hepatocyte injury.[3]

Body-building supplements may include undisclosed additives that pose their own risks of harm. A 2017 study evaluating the ingredients of 44 nutritional supplements, marketed as SARMs, found only 52% were primarily SARMs in content.[7] Of more concern, 39% of the supplements included substances unapproved by the US Food and Drug Administration, such as ibutamoren (a growth hormone secretagogue), cardarine (GW501516; a peroxisome proliferator-activated receptor-δ [PPAR-δ] agonist) and stenobolic (SR9009; a Rev-ErbA agonist).[7]

## Conclusion and recommendations

The nonmedical use of SARMs may cause severe cholestatic liver injury, potentially resulting in acute liver failure. Although this type of injury is uncommon, it has been described in several case reports. Considering the easy online availability of these body-building supplements, healthcare professionals should be aware of their potential to cause severe hepatotoxicity, which may be associated with prolonged recovery.

**Figure 1 Total serum bilirubin concentrations following withdrawal of RAD-140**



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This case emphasises the importance of clinicians taking a thorough drug history, including not only medicines, but also herbal, nutritional, dietary and body-building supplements. If a substance is suspected of causing an adverse drug reaction, a detailed history of its use is crucial, such as when it was started or stopped, any past or present use, and a timeline of its use in relation to the patient's symptoms.

A useful and free resource for clinicians on substances that can cause liver toxicity is LiverTox.[8] ≺

*Patient consent for publication of this case study was obtained by the authors.*

*Conflicts of interest: Varan Perananthan is a Clinical pharmacology trainee participant on the Australian Prescriber Editorial Executive Committee (2023–24). He was excluded from editorial decision-making related to the acceptance and publication of this case study.*

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