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Suspected Drug-Induced Hepatocellular Injury Following Use of an Unregulated Injectable Product Marketed as Retatrutide: A Case Report

Ahmed Elhassan [1], Isra Ali [2], Abu-Bekr Mohamed [3], Ahmed Mahgoub [4]

1. Endocrinology, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, ARE 2. Biomedical Sciences, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, ARE 3. Internal Medicine, Detroit Medical Center, Wayne State University, Detroit, USA 4. Internal Medicine, Tanta University Hospital, Tanta, EGY

Corresponding author: Ahmed Elhassan, aelhassan@live.com

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Abstract

Unregulated injectable preparations marketed as investigational weight-management agents raise concerns about product identity and safety. A 39-year-old man presented with fatigue, nausea, anorexia, and right upper quadrant discomfort beginning approximately 25 days after the first reported injection of a product marketed as retatrutide. At the initial clinical evaluation (day one), alanine aminotransferase (ALT) was 328 U/L and aspartate aminotransferase (AST) was 156 U/L; the R ratio was 9.87, indicating a hepatocellular biochemical pattern. Bilirubin and international normalized ratio (INR) were normal. Initial viral and autoimmune investigations were unrevealing, although hepatitis C RNA was not obtained. The patient was administered the fifth and final injection after symptom onset. His ALT declined from 328 to 118 U/L over 14 days after presentation, corresponding approximately to days five to 19 after the final reported injection, and normalized by week six. The course was compatible with, but did not establish, exposure-associated liver injury. Incomplete exclusion of alternative causes and the absence of product verification limited causal attribution.

Categories: Pharmacology, Endocrinology/Diabetes/Metabolism, Gastroenterology
Keywords: drug-induced liver injury (dili), hepatocellular injury, retatrutide, rucam score, unregulated injectable products

Introduction

Retatrutide is an investigational triple agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon receptors. A phase 2 obesity trial demonstrated substantial weight reduction and reported transient alanine aminotransferase (ALT) elevations above three times the upper limit of normal in approximately 1% of treated participants; mean ALT and aspartate aminotransferase (AST) concentrations were unchanged or decreased by week 48 [1]. Such trial findings concern the regulated investigational product, not preparations sold online under the same name. The US Food and Drug Administration has raised concerns about unapproved products marketed as retatrutide [2]. Drug-induced liver injury (DILI) requires careful assessment of exposure chronology, biochemical phenotype, competing diagnoses, and dechallenge [3,4]. We describe a suspected hepatocellular injury following use of an injectable preparation marketed as retatrutide, with emphasis on exposure verification and causal assessment.

Case Presentation

A 39-year-old man with a history of obesity (baseline BMI approximately 31.0 kg/m², calculated using a self-reported pre-injection weight of 96 kg and a height of 176 cm measured at presentation) presented with approximately eight days of fatigue, intermittent nausea, reduced appetite, and mild right upper quadrant discomfort. Day one was defined as the date of the patient's initial clinical presentation. He reported nicotine vaping but denied alcohol use, conventional cigarette smoking, and the use of prescription medications, herbal products, or dietary supplements. No diabetes, chronic liver disease, or previous unexplained aminotransferase elevation was reported. Liver tests eight months before presentation showed ALT 26 U/L, AST 22 U/L, alkaline phosphatase (ALP) 81 U/L, and total bilirubin 0.7 mg/dL.

The patient reported five once-weekly subcutaneous injections from an online-purchased multidose vial advertised as retatrutide, beginning approximately 33 days before presentation. The reported doses were 2 mg for each of the first two injections and 4 mg for each of the subsequent three injections; neither the administered doses nor the product composition was analytically verified. Symptoms began approximately 25 days after the first injection, about one week before presentation. The fifth and final injection was administered three days after symptom onset and five days before presentation. The pre-injection weight of 96 kg was self-reported; height and weight measured at presentation were 176 cm and 91 kg, respectively. The identity, concentration, purity, and sterility of the preparation were unknown.

Examination showed blood pressure 124/78 mmHg, pulse 82 beats/minute, temperature 36.7°C, and BMI 29.4 kg/m². There was mild right upper quadrant tenderness without guarding, organomegaly, ascites, or encephalopathy. Initial laboratory investigations demonstrated elevated aminotransferases with preserved bilirubin and international normalized ratio (INR) (Table *1*).

Test	Result	Reference range
ALT	328	0-45 U/L
AST	156	0-40 U/L
ALP	96	40-130 U/L
Gamma-glutamyl transferase (GGT)	62	0-60 U/L
Total bilirubin	0.8	0.2-1.2 mg/dL
Direct bilirubin	0.2	0-0.3 mg/dL
Albumin	4.3	3.5-5.2 g/dL
INR	0.9	0.9-1.1
Amylase	45	13-53 U/L
Lipase	27	13-60 U/L
Creatinine	0.9	0.7-1.3 mg/dL
Estimated glomerular filtration rate (eGFR)	111	≥90 mL/min/1.73 m²
Thyroid-stimulating hormone (TSH)	1.84	0.27-4.20 mIU/L
Ferritin	185	30-400 ng/mL
Iron	92	65-175 µg/dL
Transferrin saturation	29	20-50%
White blood cells	6.8	4.0-11.0 ×10³/µL
Hemoglobin	14.8	13.5-17.5 g/dL
Platelets	248	150-400 ×10³/µL

TABLE 1: Initial laboratory results at presentation

Reference ranges are those reported for the respective tests.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio; eGFR: Estimated glomerular filtration rate; TSH: Thyroid-stimulating hormone

The ALT was approximately 7.3 times its upper limit of normal. The R ratio was calculated using the ALT and ALP values relative to their respective upper limits of normal, as shown below.

$$R = \frac{\mathrm{ALT}/\mathrm{ALT}_{\mathrm{ULN}}}{\mathrm{ALP}/\mathrm{ALP}_{\mathrm{ULN}}} = \frac{328/45}{96/130} = 9.87$$

The resulting value of 9.87 indicated a hepatocellular biochemical pattern [5]. The GGT was minimally elevated at 62 U/L (upper limit 60 U/L).

Investigations for competing causes are summarized in Table *2*. Abdominal ultrasonography was reported to show mild hepatic steatosis without biliary obstruction (Figure *1*). Hepatitis C virus (HCV) RNA was not obtained, limiting the exclusion of acute hepatitis C. The differential diagnosis included acute viral or autoimmune hepatitis, biliary disease, muscle-related enzyme release, metabolic liver disease, and another unreported exposure. Normal creatine kinase and iron studies were reassuring but did not establish causality.

Investigation	Finding
Hepatitis A virus (HAV) IgM	Negative
Hepatitis B surface antigen (HBsAg)	Negative
Anti-hepatitis B core antigen (HBc) IgM	Negative
HCV antibody	Negative
Hepatitis E virus (HEV) IgM	Negative
HCV RNA	Not performed
Antinuclear antibody (ANA)	Negative
Anti-smooth muscle antibody	Negative
Serum IgG	Normal
Creatine kinase	Normal
Iron studies	No evidence of overload

TABLE 2: Investigations for alternative causes of liver injury

Negative serological findings do not fully exclude every acute viral infection.

HAV: Hepatitis A virus; HBsAg: Hepatitis B surface antigen; HBc: Hepatitis B core antigen; HCV: Hepatitis C virus; HEV: Hepatitis E virus; ANA: Antinuclear antibody

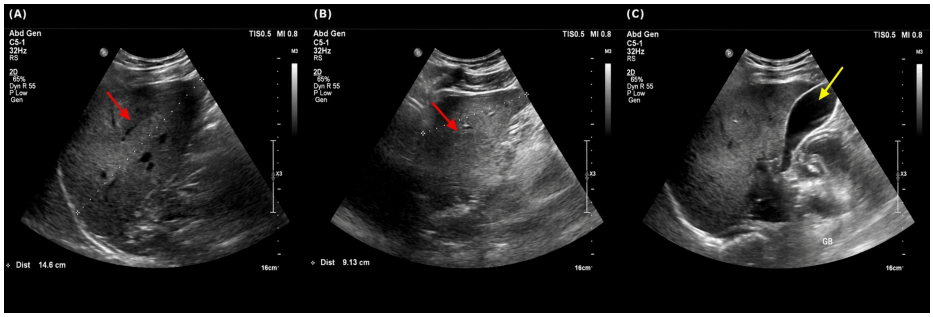


FIGURE 1: Abdominal ultrasonographic findings during the initial clinical evaluation

A: Longitudinal view of the right hepatic lobe measuring 14.6 cm, with a red arrow indicating the hepatic parenchyma; B: Left hepatic lobe measuring 9.13 cm, with a red arrow indicating the hepatic parenchyma; C: Ultrasonographic view of the liver and gallbladder, with a yellow arrow identifying the thin-walled, anechoic gallbladder. The accompanying ultrasound report described mild hepatic steatosis without biliary obstruction.

The patient reported no further injections after the fifth dose, administered approximately five days before presentation. Hepatology follow-up was arranged, and serial outpatient testing showed ALT decreasing from 328 to 118 U/L over the first two weeks after presentation (64.0%), reaching 32 U/L by week six (Table *3* and Figure *2*). The patient described gradual improvement of symptoms after discontinuation. Clinical follow-up continued until liver biochemistry normalized at week six, when follow-up was concluded. No rechallenge occurred, and no vial was retained for chemical analysis. The suspected adverse event was not formally reported to a pharmacovigilance authority.

Parameter	Week zero	Week one	Week two	Week four	Week six
ALT (U/L)	328	224	118	54	32
AST (U/L)	156	104	61	34	25
ALP (U/L)	96	94	90	87	85
Total bilirubin (mg/dL)	0.8	0.8	0.7	0.7	0.7

TABLE 3: Serial liver biochemical results during follow-up

Week zero corresponds to day one and the initial clinical evaluation, and subsequent weeks are measured from that date.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase

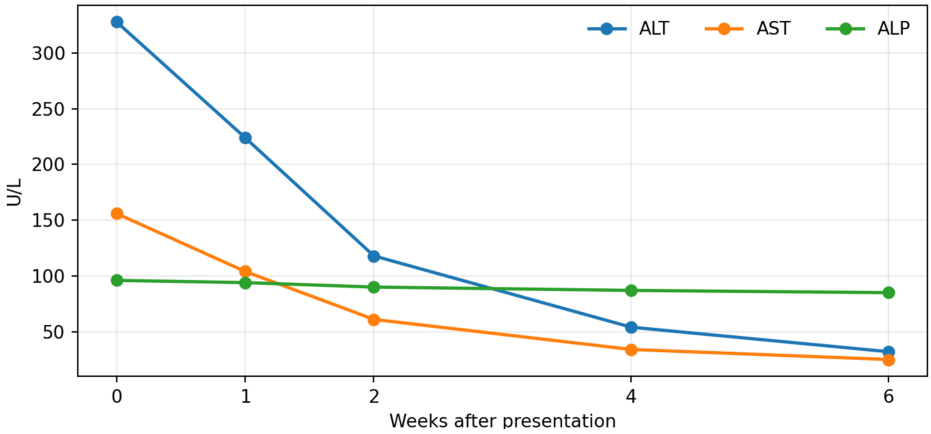


FIGURE 2: Serial liver enzyme concentrations at presentation (week zero) and at weeks one, two, four, and six after presentation

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase

Discussion

Published clinical reports involving products marketed as retatrutide outside regulated clinical trials remain limited. A case report described metabolic complications following use of an online-sourced product marketed as retatrutide [6]. The Victorian Department of Health in Australia also reported six cases of acute liver injury associated with unapproved products labeled as retatrutide [7]. These reports highlight the potential risks of unregulated preparations but do not establish the composition of the products or a causal relationship with retatrutide itself.

Published case reports describe rare liver injury temporally associated with semaglutide [8,9] and tirzepatide [10-12]. One semaglutide report documented worsening liver tests following rechallenge [8]. These observations concern different agents and do not establish the composition or hepatotoxicity of a vial marketed as retatrutide.

The R ratio of 9.87 indicates a hepatocellular biochemical pattern, not a confirmed cause. Normal bilirubin and INR at presentation were reassuring, while mild steatosis and weight loss could confound attribution [3-5,13]. The biochemical injury was characterized by an ALT elevation of approximately 7.3 times the upper limit of normal, without hyperbilirubinemia, coagulopathy, or clinical features of hepatic failure at presentation. Although the aminotransferase elevation was clinically significant, the available findings did not establish severe liver injury. The patient was not hospitalized, and no life-threatening complications or other serious outcomes were documented. The decline in ALT following discontinuation was consistent with biochemical improvement after withdrawal, although this observation alone cannot establish causality because other causes of acute liver injury may resolve spontaneously [14].

The marketed name does not verify product identity. Potential explanations include an undeclared ingredient, impurity, dosing discrepancy, the intended compound, or an unrelated illness. The safety profile

of regulated investigational retatrutide cannot be extrapolated to an untested vial [1,2,15,16]. Clinical assessment of unexplained aminotransferase elevation should include direct questions about online-purchased injectables and other nonprescription exposures, while distinguishing a marketed product name from analytically verified contents.

Limitations include the absence of liver tests immediately before exposure, incomplete evaluation for alternative viral causes (including HBV DNA, HCV RNA, and additional HEV testing), lack of analytical identification of the injected preparation, and potential confounding from hepatic steatosis and weight loss. Application of the updated Roussel Uclaf Causality Assessment Method (RUCAM) yielded a score of 2 (unlikely), comprising +2 for time to onset, +2 for biochemical improvement after withdrawal, −2 for incomplete exclusion of alternative causes, and 0 for the remaining domains [17]. The dechallenge assessment was based on the first available ALT measurement, obtained five days after the final injection; therefore, the biochemical peak may have preceded presentation. The low causality score and unknown product composition prevent confident attribution of the liver injury to the marketed product.

Conclusions

This case highlights the challenges of evaluating suspected hepatocellular injury following exposure to an unregulated injectable preparation marketed as retatrutide. The temporal relationship and subsequent improvement in liver biochemistry raised concern for an exposure-associated event, but the incomplete exclusion of alternative causes and the absence of analytical product verification prevented confident causal attribution. Clinicians evaluating unexplained aminotransferase elevations should specifically inquire about injectable preparations purchased online, as patients may not regard these products as medications. Careful documentation of exposure history, systematic investigation of competing diagnoses, and serial biochemical monitoring are essential. The findings also emphasize the importance of distinguishing the safety of regulated investigational medicines from that of unverified preparations marketed under the same name.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ahmed Elhassan, Ahmed Mahgoub, Isra Ali

Acquisition, analysis, or interpretation of data: Ahmed Elhassan, Abu-Bekr Mohamed

Drafting of the manuscript: Ahmed Elhassan, Abu-Bekr Mohamed

Critical review of the manuscript for important intellectual content: Ahmed Elhassan, Ahmed Mahgoub, Isra Ali

Supervision: Ahmed Elhassan

Disclosures

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