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ROXADUSTAT-ASSOCIATED CHOLESTATIC JAUNDICE IN HAEMODIALYSIS PATIENTS WITH POSITIVE RECHALLENGE

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ABSTRACT

Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is widely used for anaemia in chronic kidney disease. While pivotal trials reported low risks of transaminase elevations, detailed clinical case reports substantiating a causal link with cholestatic jaundice remain scarce. We report a series of four haemodialysis patients who developed cholestatic jaundice after roxadustat initiation, characterized by predominant elevations of direct bilirubin and bile acids with persistently normal transaminases. Notably, two patients had positive rechallenges. Common causes of cholestasis were excluded, and biochemical recovery occurred after drug discontinuation. This case report suggests a causal association between roxadustat and cholestatic jaundice in haemodialysis patients and highlights the value of monitoring cholestatic parameters during therapy.

KEYWORDS

Roxadustat, cholestatic jaundice, HIF-PHI, haemodialysis

LEARNING POINTS

- This case series provides clinical evidence supporting a causal association between roxadustat and cholestatic jaundice in haemodialysis patients, warranting clinical awareness of this potential adverse effect.

INTRODUCTION

Roxadustat, an oral hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor (PHI), effectively raises and maintains haemoglobin levels in chronic kidney disease patients[1,2]. Although pivotal trials have reported low rates of hepatocellular injury (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] elevations) associated with roxadustat[1-3], and a recent signal detection study based on the Japanese Adverse Drug Event Report (JADER) database identified "jaundice" and

"hyperbilirubinemia" as potential adverse events[4], detailed clinical characterization and confirmation of causality through rechallenge remain absent. Herein, we report four maintenance haemodialysis patients who developed cholestatic jaundice with persistently normal transaminases after roxadustat initiation, including one with three positive rechallenges — the first such report in this population.

CASE DESCRIPTION

Case 1: four cholestatic episodes with three positive rechallenges

Baseline: A 59-year-old man on haemodialysis, with hypertension, chronic heart failure (CHF), had negative hepatitis B virus (HBV) and hepatitis C virus (HCV). The only two pre-roxadustat liver tests (May and December 2020) showed γ-glutamyl transferase (GGT) elevations (88 and 171 U/l; reference 7-45 U/l). Direct bilirubin (DBIL) was 8.3 µmol/l (reference 0.1-6.8 µmol/l) with total bilirubin (TBIL) 20.5 µmol/l (reference 2-20.5 µmol/l) in May 2020, but both normalized by December 2020. Total bile acid (TBA), cholylglycine (CG), alkaline phosphatase (ALP), ALT, and AST were consistently normal. Abdominal ultrasound was unremarkable.

Initial episode (August 2022 - January 2023): Due to suboptimal anaemia control, therapy was switched to roxadustat (100 mg tiw) in August 2022. In January 2023, asymptomatic dialyzer discoloration occurred, with laboratory tests showing cholestatic jaundice (TBIL 117.6 µmol/l, DBIL 82.7 µmol/l, GGT 113 U/l, CG 10.2 µg/ml [reference <2.7 µg/ml]; ALP, ALT, and AST were normal). HBV/HCV and biliary obstruction were excluded. Roxadustat was discontinued, and the jaundice resolved.

Three rechallenges: For refractory anaemia, roxadustat was restarted on three subsequent occasions. The first rechallenge (100 mg tiw in March 2023) and second rechallenge (50 mg tiw from July 2023, escalated to 100 mg tiw in October 2023) each led to jaundice recurrence 1 month after reaching 100 mg tiw. The third rechallenge (100 mg tiw in October 2024) led to recurrence at 14 days. Each episode showed the same cholestatic pattern — isolated elevation of direct bilirubin and bile acids with normal transaminases — which resolved after drug withdrawal *(Fig. 1)*. After the third rechallenge, roxadustat was permanently discontinued.

Outcome: The patient died in January 2025 from a motor vehicle accident.

Case 2: delayed recognition and protracted recovery

Baseline: A 76-year-old man on haemodialysis with hypertension, CHF, and secondary hyperparathyroidism (SHPT) had negative HBV/HCV. Multiple pre-treatment tests (December 2019 to March 2022) showed normal TBIL, DBIL, GGT, ALT, and AST. ALP had mild intermittent elevations (peak 151 U/l). TBA was elevated twice (21.4 and 21.9 µmol/l; reference 0-12 µmol/l) and CG once (3.3 µg/ml). The final test before roxadustat (March 2022) was completely normal. Abdominal imaging was normal.

First cycle (August 2022 - June 2023): Roxadustat (100 mg tiw) was started in August 2022. Two weeks later, early biochemical changes (CG 19.4 µg/ml) appeared, progressing to overt jaundice by September 6: TBIL 62.6 µmol/l, DBIL 40.4 µmol/l, TBA 24.5 µmol/l, CG 31.2 µg/ml; GGT, ALP, ALT, and AST were normal. Imaging excluded biliary obstruction. Despite these abnormalities, roxadustat was continued, with only transient fluctuation of bilirubin and CG. On September 27, the drug was discontinued because of haemoglobin overshoot (132 g/l) — not because of liver concerns. By December 27, TBIL and CG had normalized; DBIL remained mildly elevated (10.6 umol/l), and GGT was 98 U/l.

During the subsequent 6 months off roxadustat (January to June 2023), liver tests returned to baseline except for elevated GGT.

Second cycle (June - December 2023): For recurrent anaemia, roxadustat (100 mg tiw) was restarted on June 5. Cholestasis recurred, but the drug was continued despite rising bilirubin and bile acids. It was only discontinued on September 7, when marked dialyzer discoloration and a surge in TBIL to 119.2 µmol/l (DBIL 91.5 µmol/l) occurred. ALT and AST were consistently normal throughout. After withdrawal, recovery was protracted (~12 weeks), with all liver tests returning to normal by December 12 *(Fig. 2)*.

Outcome: The patient died from severe infection on December 31, 2023.

Case 3: severe symptomatic cholestasis – rechallenge unmonitored

Baseline: A 61-year-old man was on haemodialysis with SHPT, idiopathic thrombocytopenia (brief steroid therapy in 2018, no long-term use), and hypertension. HBV and HCV were negative. Pre roxadustat liver tests were unremarkable except for ALP 323 - 1146 U/l.

Initial episode (September 2022 - January 2023): Roxadustat (100 mg tiw) was started on September 24. Two weeks later, isolated elevations of CG (10.4 µg/ml) and

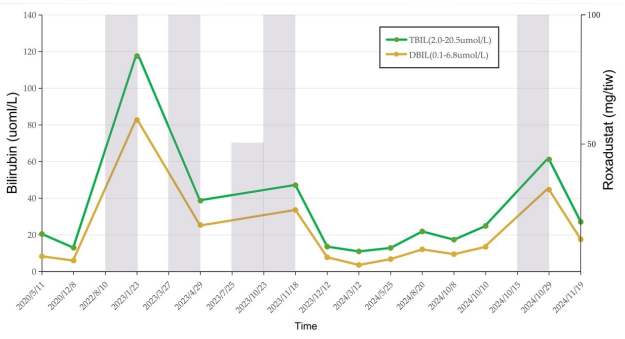


Figure 1. *Temporal relationship between roxadustat exposure and bilirubin levels in case 1. Gray shaded areas indicate periods of roxadustat administration and dosage. Green and orange lines represent total bilirubin (reference: 2.0–20.5 µmol/l) and direct bilirubin (reference: 0.1–6.8 µmol/l), respectively. The figure demonstrates four episodes of cholestatic jaundice following roxadustat exposure.*

Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin.

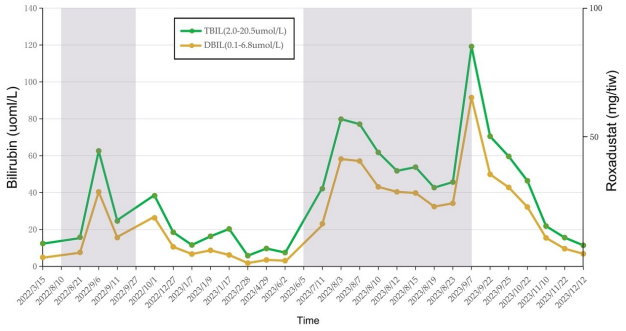


Figure 2. *Temporal relationship between roxadustat exposure and bilirubin levels in case 2. Gray shaded areas indicate periods of roxadustat administration and dosage. Green and orange lines represent total bilirubin (reference: 2.0–20.5 µmol/l) and direct bilirubin (reference: 0.1–6.8 µmol/l), respectively. The figure demonstrates two episodes of cholestatic jaundice following roxadustat exposure.*
Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin.

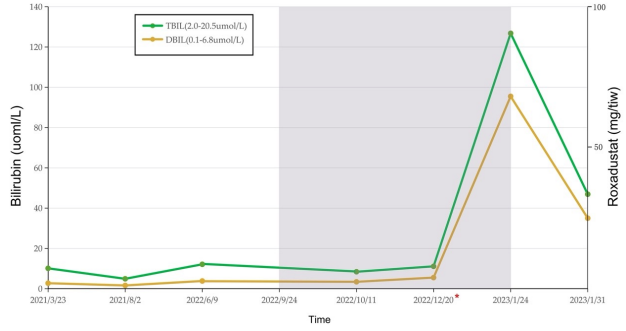


Figure 3. *Temporal relationship between roxadustat exposure and bilirubin levels in case 3 (first exposure only). Gray shaded areas indicate periods of roxadustat administration and dosage. Green and orange lines represent total bilirubin (reference: 2.0–20.5 µmol/l) and direct bilirubin (reference: 0.1–6.8 µmol/l), respectively. The red star (December 20, 2022) indicates the onset of behavioral changes (confusion, self-talk, repetitive actions). The figure demonstrates a single episode of cholestatic jaundice following roxadustat exposure. A subsequent rechallenge in March 2023 was performed but no laboratory data were available; therefore, this period is not shown in the figure.*
Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin.

TBA (18 µmol/l) were noted. On December 20, the patient developed behavioural changes (confusion, self-talk, repetitive actions). Liver tests showed GGT 66 U/l and CG 4.1 µg/ml, with normal bilirubin and transaminases. Despite these abnormalities, roxadustat was continued. By January 24, yellow dialyzer discoloration appeared, and jaundice was confirmed: TBIL 126.8 µmol/l, DBIL 95.5 µmol/l, CG 22.3 µg/ml; GGT, ALT, and AST remained normal. Abdominal imaging showed no obstruction. Roxadustat was stopped, leading to rapid improvement by January 31 and resolution of behavioural changes *(Fig. 3)*.

Rechallenge attempt (March - May 2023): For recurrent anaemia, roxadustat was restarted (100 mg tiw) on March 27. No liver tests were performed during this second exposure, and no clinical jaundice was observed. The drug was discontinued on May 18 for unspecified reasons.

Outcome: After final discontinuation, no jaundice occurred. Quarterly tests (December 2023 to June 2025) consistently showed normal liver function except for ALP. The patient was lost to follow-up after relocating in July 2025.

Case 4: acute cholestatic jaundice with underlying polycystic liver disease

Baseline: A 54-year-old woman was on maintenance haemodialysis due to polycystic kidney disease, with concomitant polycystic liver disease (PLD) and SHPT. Pre roxadustat monitoring (December 2023 to August 2024) showed elevated ALP (163-686 U/l) and GGT (138-274 U/l). TBIL, DBIL, and CG were normal. HBV/HCV were negative.

Onset and management (August - October 2024): Roxadustat 100 mg tiw was started in August 2024. Two months later, she developed right upper quadrant pain, followed by jaundice (76.8 µmol/l, DBIL 54.5 µmol/l, CG 4 µg/ml; GGT, ALT, and AST were normal). Abdominal imaging showed stable PLD without biliary obstruction. Roxadustat was stopped immediately. Abdominal pain resolved within 6 days. Liver function improved progressively, with TBIL/DBIL and CG normalizing by January 10, 2025.

Outcome: No rechallenge was performed. The patient had no recurrence of pain or jaundice. During quarterly follow-up through September 2025, liver tests returned to baseline *(Fig. 4)*.

DISCUSSION

The causal relationship between roxadustat and cholestatic jaundice in haemodialysis patients was supported by a clear temporal association, clinical or biochemical improvement after each withdrawal, positive rechallenge, and exclusion of alternative causes. To

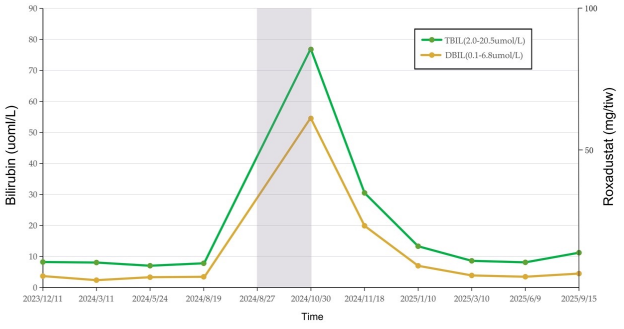


Figure 4. *Temporal relationship between roxadustat exposure and bilirubin levels in case 4. Gray shaded areas indicate periods of roxadustat administration and dosage. Green and orange lines represent total bilirubin (reference: 2–20.5 µmol/l) and direct bilirubin (reference: 0.1–6.8 µmol/l), respectively. The figure demonstrates a single episode of cholestatic jaundice following roxadustat exposure. No rechallenge was performed.*
Abbreviations: TBIL, total bilirubin; DBIL, direct bilirubin.

quantify this relationship, we applied the Naranjo adverse drug reaction probability scale to all four cases[5]. The scores were 9 (definite) for cases 1 and 2, and 7 (probable) for cases 3 and 4. All patients presented with cholestatic jaundice and elevated bile acids without transaminase or liver specific ALP elevation — a pattern indicating impaired excretory function rather than acute hepatocellular injury[6]. Nevertheless, cholestasis itself can initiate inflammatory liver injury[7], warranting clinical attention. To date, only one other case report has described roxadustat-associated jaundice in a peritoneal dialysis patient who had a mixed pattern with elevated transaminases and haemolysis[8] — a phenotype distinct from the pure cholestatic pattern observed in our four patients.

The precise mechanism underlying roxadustat-associated cholestatic jaundice remains poorly understood. The biological plausibility of this adverse effect is supported by the established role of HIF signalling in regulating hepatobiliary function and bile acid homeostasis[9]. Hypoxia has been shown to downregulate key hepatobiliary transporters, including the bile salt export pump and multidrug resistance-associated protein 2[10]. By stabilizing HIF-α, roxadustat may mimic this hypoxic response, potentially impairing bile acid secretion and leading to intrahepatic cholestasis.

Of note, cases 1, 2, and 4 all exhibited some form of pre-existing hepatobiliary abnormality before roxadustat exposure. These findings suggest that such subtle or underlying cholestatic dysfunction may be a potential predisposing factor that could render some individuals more susceptible to roxadustat-associated cholestasis. In addition, the abdominal pain in case 4 may be associated with roxadustat-induced enlargement of hepatic cysts, though this remains a speculative inference. Previous study has indicated that roxadustat may promote cyst growth and disease progression in polycystic kidney disease[11]. A markedly shorter latency of jaundice recurrence after roxadustat rechallenge in case 1 (from 5 months to 2 weeks) is another clinical observation for which the underlying mechanism remains unclear.

CONCLUSION

This case report provides clinical evidence supporting a causal association between roxadustat exposure and cholestatic jaundice in haemodialysis patients. Our findings highlight this underrecognized adverse event and call for increased clinical awareness and further investigation.

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