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CASE REPORT

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Drug-induced liver injury associated with savolitinib: a novel case report and causality assessment

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Abstract

Background Savolitinib, a small molecule inhibitor, has gained approval as the inaugural medication in China that specifically targets MET kinase. Patients with advanced non-small cell lung cancer (NSCLC) who show MET exon 14 skipping now have a new and innovative treatment option available.

Case report In this case report, we describe a patient who experienced drug-induced liver injury (DILI) due to the administration of savolitinib. After being prescribed with savolitinib (400 mg per day, oral), a 73-year-old male diagnosed with stage IV NSCLC with MET exon 14 skipping mutation experienced an increase in liver enzymes and bilirubin levels according to his laboratory tests conducted one month later. Following a 14-day course of hepatoprotective medication, the liver function reverted back to its normal state. After receiving savolitinib (200 mg per day, oral) for one week, the patient was once again diagnosed with severe liver impairment. Then savolitinib was discontinued and received treatment with hepatoprotective drugs for one week. Following the restoration of normal liver function, another attempt was made to administer a small amount of savolitinib (100 mg per day, oral). Thus far, the patient has been followed up and there has been no recurrence of liver damage. Additionally, the lung CT scan revealed ongoing tumor shrinkage with no apparent indications of spreading or metastasis. The Roussel Uclaf Causality Assessment Method (RUCAM) determined that savolitinib was "highly probable" cause of DILI. Moderate-severe was determined to be the extent of DILI severity.

Conclusion To the best of our understanding, this is the initial instance of DILI resulting from the use of savolitinib as a standalone treatment in a real-world setting. During the administration of savolitinib, healthcare professionals should carefully consider the potential occurrence of DILI. Administering the patient with a small amount of savolitinib resulted in a remarkable response against the tumor, leading us to speculate that the effectiveness of savolitinib might be associated with its plasma concentration. Studying the pharmacokinetics and pharmacodynamics (PK/PD) of savolitinib is beneficial for tailoring and accurately prescribing the medication to each individual.

Keywords Savolitinib, Targeted therapy, Hepatic failure, Non-small cell Lung Cancer, Case report

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Introduction

Lung cancer remains the leading cause of cancer morbidity and mortality worldwide. Non-small Cell Lung Cancer (NSCLC), which makes up 80-90% of lung cancers [1]. Mesenchymal epithelial transformation factor (MET) exon 14 skipping is a rare oncogenic driver in NSCLC, while MET exon 14 alterations were first identified in small cell lung cancer (SCLC) [2], subsequent research showed that these alterations are more frequently observed in NSCLC, with a prevalence of 3–4% [3–6]. In recent times, a number of anti-MET targeted treatments (MET exon 14 skipping mutations) have been given approval by the FDA, including carmatinib [7] and tepotinib [8]. Clinical trials have demonstrated that targeted therapy against MET has yielded positive outcomes in patients with NSCLC who have mutations involving the skipping of exon 14 in the MET gene [9].

Approved by the CFDA, savolitinib is now accessible in 2021 for the treatment of metastatic NSCLC in patients who have experienced progression or cannot endure platinum-based chemotherapy, specifically targeting those with MET exon 14-skipping alterations [10]. In China, savolitinib is the initial authorized inhibitor of MET kinase, designed as a small molecule, that specifically targets MET exon 14 skipping. This offers advanced NSCLC patients a fresh alternative for treatment. To date, there have been no reports of drug-induced liver injury (DILI) resulting from the use of savolitinib as a standalone treatment in real-world settings.

This study presents the initial instance of DILI linked to the use of Savolitinib as the sole treatment in a real-world setting, characterized by a significant 70-fold elevation in aminotransferase levels.

Case report

A 73-year-old man, who had been in good health, received a diagnosis of stage IV NSCLC with MET exon 14 skipping mutation on 18 April 2023. Figure 1A displays a mass measuring 68×56 mm located in the lower lobe of the right lung. He refuted having any previous medical conditions including high blood pressure, diabetes, heart disease, liver ailments, or contagious illnesses like tuberculosis. The patient did not have any previous cases of cancer or other illnesses in their family, nor did they have any past drug or food allergies. The patient has experienced intermittent cough, dry cough without phlegm, chest tightness, chest pain, difficulty breathing, low-grade fever, night sweats, hoarseness, palpitations, and other forms of discomfort since the beginning of the illness. On April 27 2023 (Day 0), his liver function was within the normal range (Fig. 2A), the laboratory results showed alanine aminotransferase (ALT) at 35 U/L (normal range, 7–40 U/L), aspartate aminotransferase (AST) at 27 U/L (normal range, 13–35 U/L), alkaline phosphatase (ALP) at 73 U/L (normal range, 50–135 U/L), total

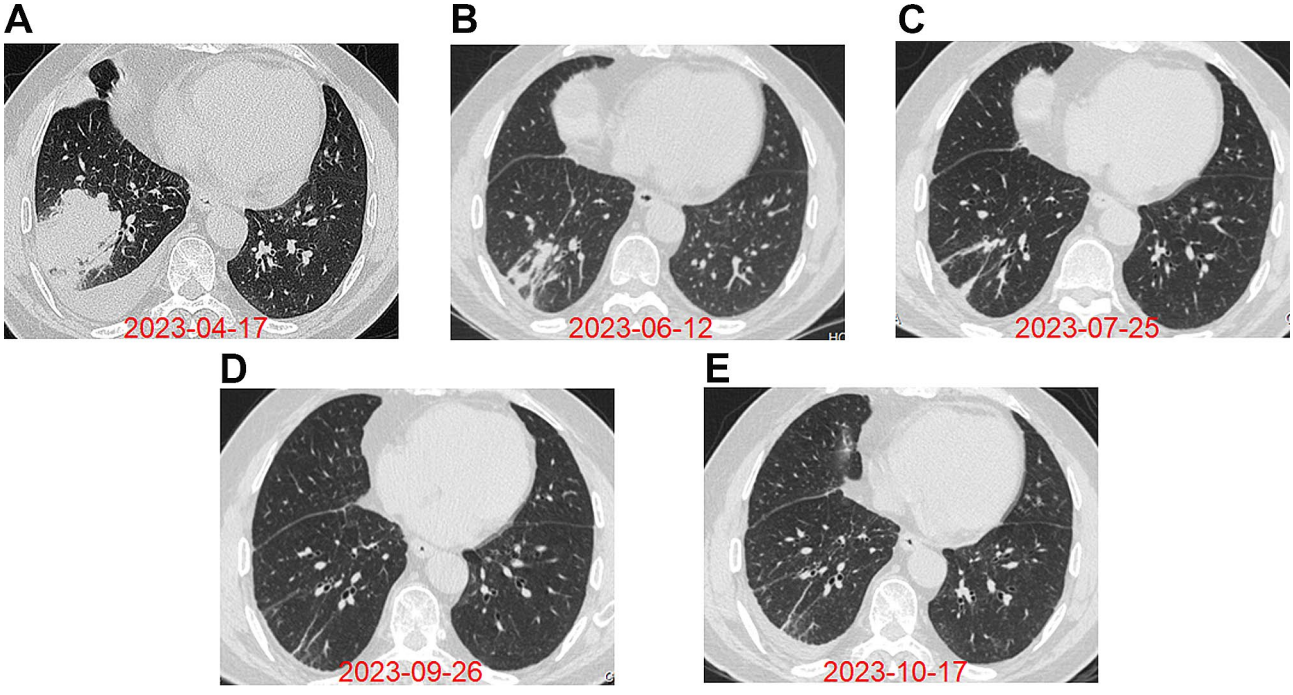

Fig. 1 Comparison of chest CT scans pre- and post-treatment with savolitinib: (**A**) Initial chest CT scan prior to the administration of savolitinib, showing the primary tumor mass and any potential signs of metastasis. (**B**) CT scan results after the commencement of savolitinib treatment, highlighting the notable decrease in tumor size and the absence of tumor progression or spread. (**C**) CT scan after three month, showing continued tumor reduction. (**D**) CT scan after five months, showing stable disease. (**E**) CT scan after six months, showing further tumor reduction with no new lesions

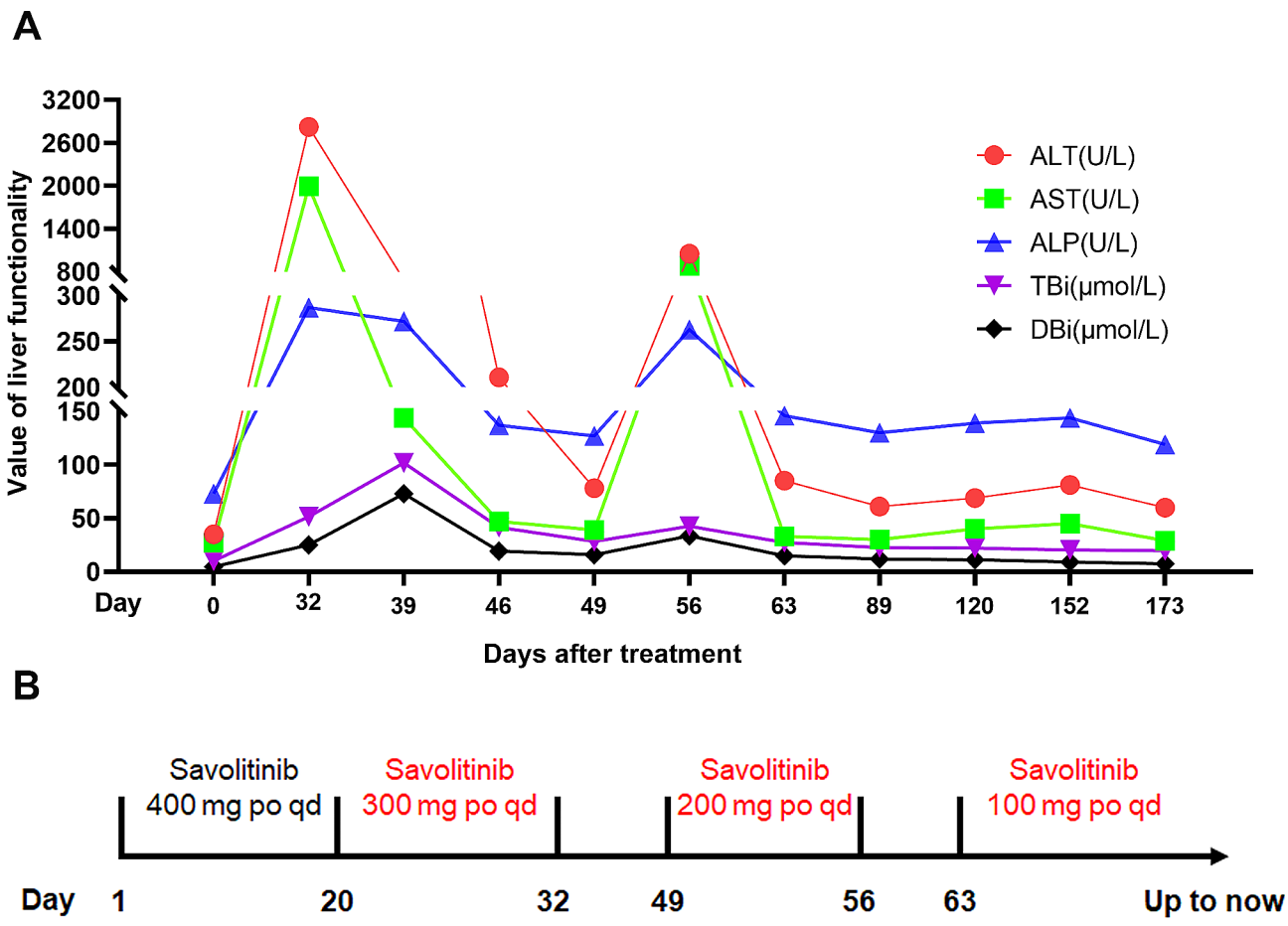

Fig. 2 Timeline of Drug Therapy and Liver Function Changes: (**A**) Liver enzyme and bilirubin levels over time, with numerical scale indicating days after the start of treatment. (**B**) Dosage adjustments and discontinuation of savolitinib. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBil), and direct bilirubin (DBil). Note: Specific days are indicated for clarity: Day 0 (April 27, 2023), Day 1 (April 28, 2023), Day 32 (May 29, 2023), Day 33 (May 30, 2023), Day 49 (June 15, 2023), Day 56 (June 22, 2023), Day 63 (June 29, 2023), Day 93 (July 29, 2023), Day 152 (September 26, 2023), and Day 173 (October 17, 2023)

bilirubin (TBil) at 10.1 μmol/L (normal value, 3.4–20.4 μmol/L), and direct bilirubin (DBil) at 4.6 μmol/L (normal value, 0–6.8 μmol/L).The following day (Day 1), he was administered savolitinib (400 mg per day, oral) for targeted therapy, based on his weight of 48 Kg (less than 50 Kg).The patient experienced back pain and discomfort in the legs as a result of taking oral medication. Consequently, the patient independently decided to decrease the dosage (300 mg per day, oral) starting from May 17 2023 (Day 20). Subsequently, the symptoms of discomfort showed improvement following the reduction in dosage.

On May 29, 2023 (Day 32), the patient's lab tests revealed significant liver damage with ALT levels of 2822 U/L, AST levels of 1994 U/L, ALP levels of 287 U/L, TBil levels of 51.4 μmol/L, and DBil levels of 25.0 μmol/L. The patient's test results were negative for anti-HAV-IgM (hepatitis A virus antibody), HBsAg and HBV DNA (hepatitis B virus antigen and DNA), HCV cAg and HCV RNA (hepatitis C virus antigen and RNA), anti-HEV-IgM/IgG (hepatitis E virus antibody), as well as various autoantibodies (including antinuclear antibodies, smooth muscle antibodies, antibodies to the liver–kidney microsome type 1, antimitochondrial antibodies, antibodies to liver cytosol type 1, and antibodies to soluble liver antigen). No abnormalities are observed in abdominal ultrasound, computed tomography (CT), liver magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP), with alpha-fetoprotein (AFP) levels within the normal range of 0–7 ng/ml (2.04 ng/ml).

Probable adverse drug reactions were indicated by a Naranjo score of 5, suggesting liver injury caused by savolitinib. Based on a score of 11 [11] from the Roussel Uclaf Causality Assessment Method (RUCAM), it was concluded that savolitinib was the likely culprit for DILI. Furthermore, the classification of liver cell damage induced by Savolitinib as DILI was determined based on the guidelines for drug-induced liver injury [12, 13]. The patient declined to undergo a liver biopsy. Based on DILI

guidelines [12, 13], the severity of DILI was evaluated as moderate-severe by US DILIN severity index.

Savolitinib was discontinued on May 30 (Day 33). For a duration of 2 weeks, the patient was administered drug treatment which consisted of a daily dosage of 150 mg of magnesium isoglycyrrhizinate, 1 g of S-adenosylmethionine, and 1.8 g of glutathione, following the recommendations of the Chinese DILI guidelines [14]. By June 15, 2023 (Day 49), the patient's liver function essentially returned to normal according to the laboratory examinations(Fig. 2A). In the meantime, according to Fig. 1B, there was a notable decrease in tumor size compared to before treatment (Fig. 1A). According prescribing information, the patient must not continue taking savolitinib, but he insisted on continuing to treatment with savolitinib because of lung CT showed a great therapeutic result. Following the communication with the patient, it was ultimately determined that he could benefit from reduced quantities of savolitinib (200 mg per day, oral), in addition to the necessity of oral glutathione tablets.

Regrettably, a week following the retreatment using savolitinib, subsequent laboratory tests revealed a recurrence of severe liver damage with ALT levels reaching 1052 U/L, AST levels at 880 U/L, ALP levels at 263 U/L, TBil levels at 42.4 μmol/L, and DBil levels at 33.4 μmol/L (Fig. 2A). Because the recurrence of liver injury was caused by the re-administration of savolitinib, the updated Naranjo score was 7. After discontinuing savolitinib on June 22 (Day 56), he underwent drug treatment for one week. The treatment included daily intake of 150 mg of magnesium isoglycyrrhizinate, 1 g of S-adenosylmethionine, 1.8 g of glutathione, and three daily doses of 456 mg of polyene phosphatidylcholine. The laboratory tests on 29 June (Day 63) indicated that the patient's liver function had essentially returned to its normal state (Fig. 2A). The patient expressed a desire for treatment with savolitinib at a reduced dosage, therefore, he was administered targeted therapy with savolitinib (100 mg per day, oral) along with the additional requirement of oral glutathione tablets and polyene phosphatidylcholine capsule.

After the administration of savolitinib for a month, the lung CT scan revealed a decrease in tumor size with no signs of tumor advancement or spread (Fig. 1C). Additionally, his liver function appeared to be mostly normal (Fig. 2A). Based on imaging assessment, the patient attained a partial response (PR) and is still undergoing treatment with savolitinib and hepatic protector medication. During the follow-up appointments on September 26, 2023 (Day 152), and October 17, 2023 (Day 173), the lung CT scans (Fig. 1D-E) revealed the patient's condition remained stable (SD), with no signs of liver function deterioration (Fig. 2A). Figure 2B illustrates the application of savolitinib. Throughout the entire treatment, the patient expressed concurrence with the clinician regarding the hazards, medication, and course of action. He is currently being followed up.

Discussion

Careful assessment is necessary for diagnosing DILI, which is determined by excluding other possible diagnoses. As previously stated, the individual stated that there was no familial background in this instance. Following treatment with Savolitinib, he maintained his sanity and experienced a shift in tiredness, decreased appetite, and increased levels of liver enzymes. Imaging of the liver revealed no abnormalities. During hospitalization [15], the individual did not exhibit any signs of fever or lymphadenopathy, and there were no observed extrahepatic manifestations of HEV infection, particularly neurological damage. All laboratory measurements for viral hepatitis and autoantibodies yielded negative results. The aforementioned factors result in an unsupported determination of viral hepatitis and autoimmune hepatitis [16]. No evidence of steatosis or cirrhosis was observed in the liver imaging. The diagnosis of steatohepatitis was subsequently ruled out [17]. Exclusion of Wilson disease was possible [18] as the patient did not exhibit the typical presentations of Kayser-Fleischer rings and neuropsychiatric disturbances, which are commonly associated with this condition, and also had no reported family history. What is more important, the liver injury recurred after the patient restarted treatment with savolitinib on June 15. Subsequently, the occurrence of liver damage caused by savolitinib was ultimately confirmed, as indicated by a Naranjo score of 7 and a RUCAM score of 11.

The liver is responsible for the majority of the metabolism of Savolitinib through drug-metabolizing enzymes [19]. After evaluating with RUCAM, Naranjo's probability scale for adverse drug reactions, and analyzing clinical, laboratory, and imaging characteristics, the diagnosis of liver injury caused by savolitinib was highly probable in this case. The DILI instance was primarily characterized by a 70-fold surge in aminotransferase levels along with an elevation in bilirubin, denoted as a grade 4 unfavorable occurrence. Due to the infrequent occurrence of severe DILI as a complication of savolitinib treatment, there has been minimal focus on monitoring liver function. Liver injury was not identified until the patient underwent regular monthly laboratory examinations. Hence, it is imperative to monitor liver function throughout the treatment to promptly identify any signs of liver damage.

Moreover, there is a concern regarding potential heightened toxicity caused by interactions between drugs. Savolitinib metabolism heavily relies on essential cytochrome P450 enzymes, as CYP1A2, CYP3A4/5, and

CYP2D6 [19]. To prevent a higher chance of drug toxicity, it is advisable for patients who are on savolitinib to refrain from using CYP450 inhibitors or CYP450 substrates simultaneously. In this scenario, starting from the beginning until the diagnosis of DILI, the patient exclusively consumed savolitinib, thereby ruling out the possibility of any other medication-related liver damage.

Savolitinib does not cause significant liver damage as a side effect [20, 21]. In the savolitinib group, a phase 2 trial [20] demonstrated the lowest occurrence of all adverse events and grade 3 or 4 adverse events compared to sunitinib, cabozantinib, and crizotinib. Approximately 17% of the patients encountered adverse events of any grades involving increased liver enzymes (ALT, AST), while none of the patients encountered a severe grade 3 adverse event related to ALT/AST elevation. Regarding serious adverse events related to treatment, there were no instances of liver injury such as increased levels of liver enzymes and bilirubin observed in any of the patients [20–22]. In general, the occurrence of serious aminotransferase abnormalities and DILI with savolitinib demonstrated a reduced likelihood. In clinical trials, there were mostly temporary elevations in aminotransferase levels [20–22], which could be potentially associated with hepatotoxic events caused by savolitinib. And we didn't find any reports of hepatic injury associated with savolitinib after consulting the literature.

According to the information provided for prescribing, adverse events related to savolitinib can be effectively managed by interrupting treatment, reducing the dosage, and/or utilizing additional drug therapy. Nevertheless, in this investigation, savolitinib caused severe liver toxicity of grade 4, yet decreasing the dosage did not compromise the effectiveness of savolitinib. Notably, the patient achieved a partial response in this study by maintaining a low dosage of savolitinib (100 mg per day, oral). This implies that decreasing the dosage could be the optimal approach to alleviate the adverse effects caused by savolitinib. Additionally, this instance serves as a prompt that the healing impact of savolitinib could potentially be associated with its level in the bloodstream. Our next objective, as a clinical pharmacist, is to build a population pharmacokinetic model for savolitinib. Studying the pharmacokinetics and pharmacodynamics (PK/PD) of savolitinib is beneficial for tailoring and accurately prescribing the medication to each individual.

However, this study still has certain constraints. Diagnosing DILI remains challenging due to the absence of pathological examination and serological tests for Epstein-Barr virus, cytomegalovirus, and reconfirmed HEV infection. Due to the absence of genetic testing, the complete investigation of the connection between genotype of drug metabolism and liver injury has not been conducted, and the precise cause of savolitinib-induced liver injury is still unknown. We didn't measure the blood concentration of savolitinib, because we haven't been establish the method for measuring the blood concentration of savolitinib.

Conclusion

As far as we know, this is the initial instance of DILI resulting from the use of Savolitinib as the sole treatment in a real-life scenario. During the treatment of Savolitinib, clinicians should be especially mindful of the potential occurrence of DILI. After administering a small amount of savolitinib to the patient, we observed a significant antitumor response. It is our belief that the effectiveness of savolitinib in treating the tumor may be associated with its concentration in the bloodstream. Studying the PK/PD of savolitinib is beneficial for tailoring and accurately prescribing the medication to each individual.

Author contributions

The design was conceived and the manuscript was written by FFG and CL. LXL and PY revised the manuscript. After reviewing the manuscript, CL took on the responsibility of ensuring the completeness and accuracy of the data. The article was contributed to by all authors and the submitted version was approved by them.

Data availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

Consent was obtained from the individual(s) in writing for the publication of any potentially identifiable images or data included in this article.

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