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CASE REPORT | LIVER

# Olaparib-Induced Immune-Mediated Liver Injury

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## ABSTRACT

Immune-mediated drug-induced liver injury can be triggered by multiple classes of medications including immunotherapies. Olaparib is a first-in-class oral inhibitor of poly (adenosine diphosphate-ribose) polymerase (an enzyme involved in DNA replication and repair) that is approved as maintenance treatment in platinum-sensitive, epithelial ovarian, tubal, or primary peritoneal cancers with breast cancer 1/2 mutation. We report the first case in the United States of an acute and severe liver injury with associated jaundice and liver synthetic dysfunction secondary to olaparib. The liver injury was resolved with drug cessation and treatment with prednisone taper.

## INTRODUCTION

Initial therapy of ovarian cancers usually consists of surgical cytoreduction and combination platinum/taxane-based chemotherapy, but most patients will relapse of their disease and require additional treatment.[1] Inhibitors of poly (adenosine diphosphate-ribose) polymerase (PARP) have been used for relapsed ovarian cancers as well as for other cancers, including breast cancer, prostate cancer, and pancreatic cancer.[2–4] Olaparib, a first-in-class oral PARP inhibitor, has been associated with transient elevations in serum aminotransferases,[5] but to date, there has been only 1 case report in Italy of severe, immune-mediated drug-induced liver injury (IM-DILI) secondary to olaparib.[6] In general, IM-DILI can lead to acute or chronic liver injury, depending on the duration of the exposure to the drug. Fever, eosinophilia, lymphadenopathy, and rash may be present but are not universal, and immunosuppression may be required if the liver injury does not improve with drug withdrawal.[7–9]

## CASE REPORT

A 56-year-old woman with a history of advanced high-grade endometrioid and serous carcinoma involving the left adnexa, right fallopian tube, peritoneum, omentum, and right diaphragm underwent neoadjuvant chemotherapy with carboplatin and paclitaxel, followed by a total abdominal hysterectomy, bilateral salpingo-oophorectomy, optimal interval debulking, and completion of adjuvant carboplatin and paclitaxel chemotherapy for a total of 6 cycles. She had a complete response but 6 months later was found to have relapsed disease, prompting retreatment with carboplatin and doxorubicin for 6 cycles, again with complete response. Because of BRCA1 mutation, she started olaparib for maintenance therapy. Three and a half months after initiation of olaparib, she was hospitalized because of a severe acute hepatocellular liver injury (alanine transaminase: 3,350 U/L, aspartate transaminase: 2,993 U/L, and alkaline phosphatase: 215 U/L) with jaundice (total bilirubin up to 11.4 mg/dL), elevated international normalized ratio (up to 2.1), and concern for impending fulminant liver failure (Table 1). Her liver tests had previously been normal up to 1 month before her hospitalization. She had no history of alcohol use or use of herbal supplements. Physical examination was notable for jaundice, mild right upper quadrant tenderness, and no hepatic encephalopathy. Computed tomography showed mild hepatomegaly with periportal edema. Laboratory work-up for infectious, metabolic, and autoimmune etiologies of liver injury was negative. Olaparib was promptly withdrawn, and oral prednisone 60 mg/d was initiated on hospital day 3. Subsequent liver biopsy was performed on hospital day 7 and revealed areas of submassive necrosis with lobular collapse, moderate to severe portal and lobular inflammation with predominantly lymphocytes, cholestasis with focal hepatocyte rosette formation, acute cholangitis with bile duct injury, ductal

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**Table 1. Liver tests and INR**

| | Day 1 | Day 2 | Day 3 | Day 7 | Day 13 | Day 20 | Day 27 | Day 34 | Day 68 |
|---|---|---|---|---|---|---|---|---|---|
| Total bilirubin (mg/dL) | 11.4 | 11.2 | 9.1 | 3.1 | 2.5 | 1.2 | 0.6 | 0.6 | 0.3 |
| Direct bilirubin (mg/dL) | 7.4 | 7.6 | 6.5 | 2.7 | 1.4 | | | | |
| AST (U/L) | 2,993 | 1,543 | 627 | 114 | 75 | 54 | 40 | 33 | 33 |
| ALT (U/L) | 3,350 | 2,406 | 1,455 | 533 | 111 | 55 | 39 | 26 | 26 |
| ALP (U/L) | 215 | 195 | 161 | 115 | 88 | 78 | 77 | 77 | 66 |
| INR | 1.9 | 2.1 | 1.81 | 1.41 | 1.1 | 0.9 | 0.9 | | |

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio.

proliferation, and ceroid-laden histiocytes consistent with IM-DILI (Figure 1). No portal fibrosis was seen. Her liver tests improved, and she was discharged home on hospital day 8. As an outpatient, she continued to have improvement of her liver chemistries with eventual normalization, and prednisone was tapered off after 4 weeks without recurrent liver injury (Figures 2 and 3). She was not rechallenged with another PARP inhibitor.

## DISCUSSION

With the increasing use of PARP inhibitors, rare toxicities are more likely to be identified. Severe liver injury has only been reported in 1 other case,[6] and the exact mechanism of injury is not well understood. There is speculation that IM-DILI, such as seen in these 2 cases of olaparib toxicity, may be related to hepatic metabolism of the culprit drugs, with reactive metabolites binding to cellular proteins or macromolecules on hepatocytes and leading to autoantibodies reacting with liver-specific antigens as well as direct toxic effect on hepatocytes.[7,8] The clinical presentation of IM-DILI can mimic autoimmune hepatitis. Affected patients may have a spontaneous remission of acute hepatitis after drug cessation or have liver damage that does not improve after drug withdrawal. In the latter situation, the use of immunosuppressive therapies may be lifesaving. Most patients with IM-DILI will have a complete response to immunosuppressive treatment and, unlike patients with idiosyncratic autoimmune hepatitis, can typically undergo rapid tapering and withdrawal of immunosuppression without relapse.[9]

DILI diagnosis remains a diagnosis of exclusion; therefore, the extensive work-up for alternative causes such as autoimmune hepatitis or infection is recommended, and liver biopsy is often necessary for confirmation. Our patient had a negative autoimmune, and infectious work-up and liver biochemical tests were consistent with a hepatocellular pattern of liver injury with an R score of 40. Roussel Uclaf Causality Assessment Method[10] score was 7, indicating a probable association, based on the temporal association of the drug with the liver injury, negative work-up for an alternative etiology, and improvement in liver biochemistries after discontinuation of olaparib, all of which favored a diagnosis of DILI. Ultimately, a liver biopsy showed histological features suggestive of immune-mediated injury. Improvement in liver chemistries is usually seen with drug discontinuation, but severe or persistent immune-mediated injury may necessitate immunosuppression. For our patient, given biochemical evidence of significant liver synthetic dysfunction concerning for risk of progression to fulminant liver failure, prednisone was initiated promptly based on the single previous published report of IM-DILI from olaparib that was responsive to prednisone.[6] Although the liver injury was much more severe for our patient than in the published case, our patient had a similar rapid improvement with drug discontinuation and prednisone. We cannot ascertain whether she may have improved with drug discontinuation alone. Likewise, the safety of rechallenge with an alternative PARP inhibitor is currently unknown.

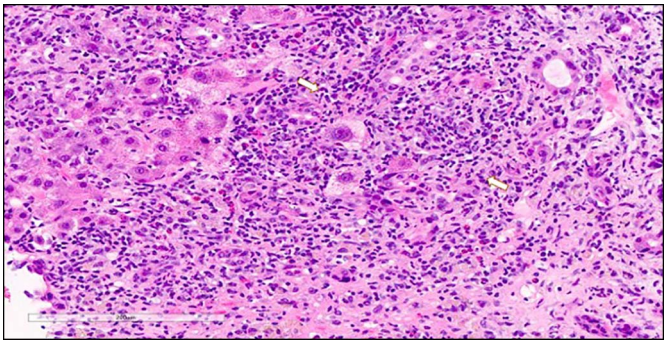

**Figure 1.** Ductular proliferation with acute cholangitis (between 2 arrows).

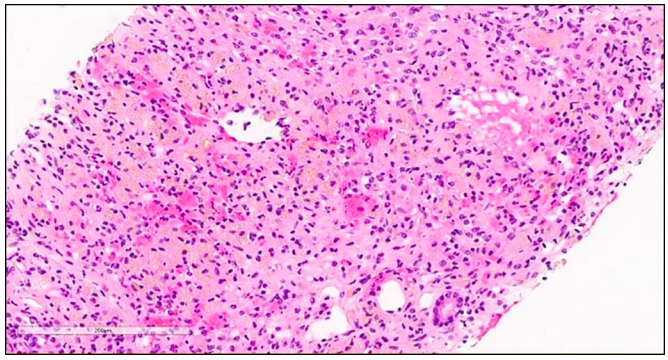

**Figure 2.** Areas of submassive necrosis with lobular collapse. Note that no viable hepatocytes are identified.

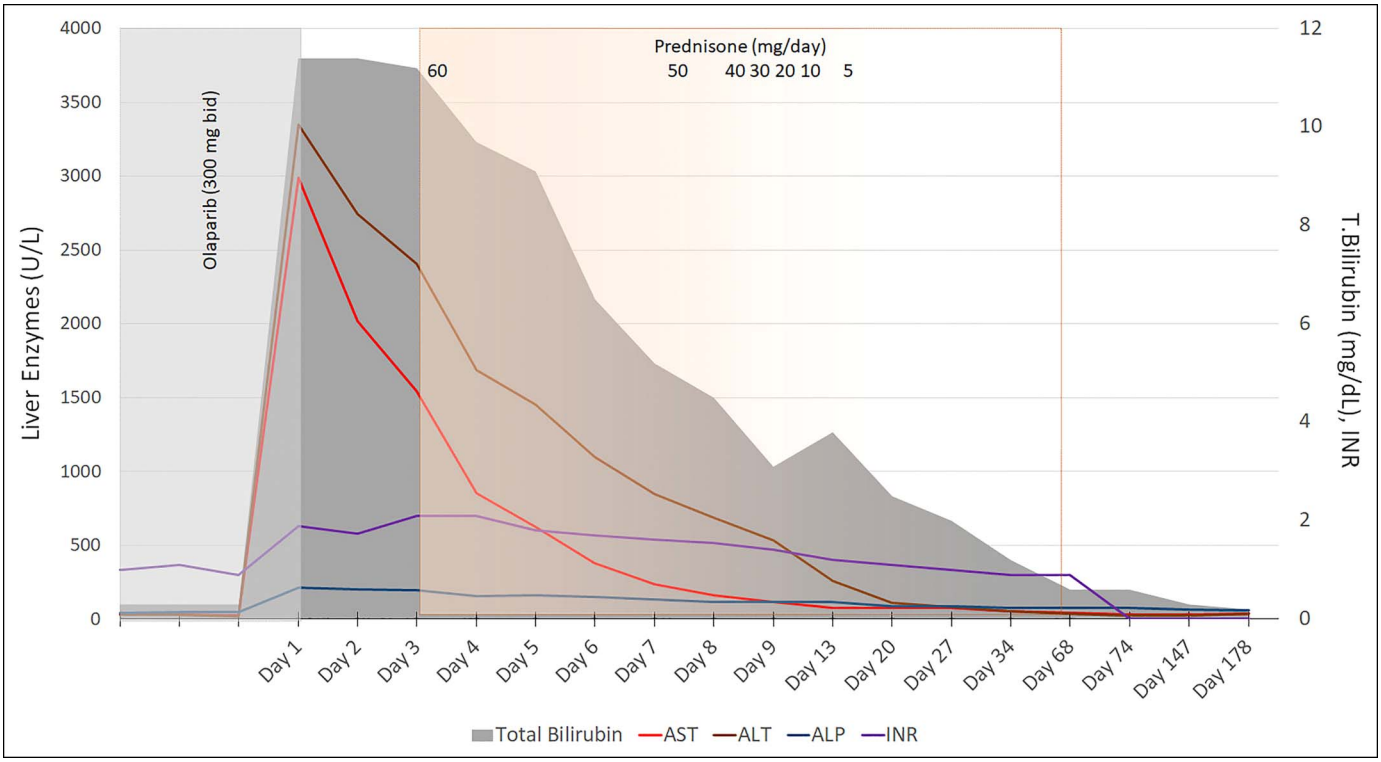


**Figure 3.** Graph of liver enzymes.

Interestingly, data suggest a protective role of PARP inhibitors in other liver diseases. In preclinical models of liver disease such as nonalcoholic steatohepatitis, PARP inhibitors attenuated liver injury secondary to a high-fat diet or alcohol through anti-inflammatory and antifibrotic effects.[11] In our patient, liver injury secondary to the PARP inhibitor was likely due to an immune response rather than from mitochondrial dysfunction and metabolic alterations, based on the histologic findings seen. In conclusion, patients with advanced ovarian cancers are increasingly being treated with molecularly targeted therapies such as PARP inhibitors that have a potential risk of idiosyncratic hepatoxicity, including IM-DILI, that requires prompt diagnosis and treatment. More research is needed to expand our understanding of the pathogenesis and risk factors for IM-DILI from PARP inhibitors and to assess the safety of alternative therapeutic options in affected patients.

## DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. M. Alshelleh is the article guarantor.

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