

# Acute liver failure requiring transplantation: A possible link to ulipristal acetate treatment?

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## Abstract

The present case describes in detail a 55-year-old woman diagnosed with acute liver injury 3 days after completion of the first treatment course with ulipristal acetate (UPA), 5 mg/day orally for uterine fibroids causing persistent bleeding (treatment duration of 109 days). Liver transplantation was performed approximately 6 weeks after UPA suspension, and a photograph of the explanted liver is presented. Of note, other common causes of acute liver injury, such as history of alcohol or other psychoactive substances abuse, viral hepatitis and autoimmune hepatitis or preexisting liver disease were all excluded. This case was reported to the European Medicines Agency (EMA) and contributed to the final recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) disclosed in January 2021. The causality assessment considered a probable case of drug-induced liver injury as a consequence of UPA treatment, and the Roussel Uclaf Causality Assessment Method (RUCAM) was scored as unlikely. Although further studies are needed aiming to avoid confounding factors, this case suggests that liver function tests should be monitored during treatment with UPA.

## KEYWORDS

case report, drug induced liver injury, European medicines agency, hepatic toxicity, metabolism, pharmacokinetics, Pharmacovigilance Risk Assessment Committee, restricted use, transplant, ulipristal acetate, updated RUCAM

## 1 | INTRODUCTION

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (SPRM) used at a dose of 30 mg as an emergency contraceptive and as a 5-mg tablet (Esmya<sup>®</sup>) for the treatment of women with symptomatic uterine fibroids; the latter use is limited to four treatment courses of 12 weeks (approximately 3 months) each.<sup>1–3</sup> Very few and non-severe cases of elevated liver enzymes were reported during clinical trials with UPA in nearly 2000 women.<sup>4,5</sup> However, after the commercial release of Esmya<sup>®</sup>, cases of hepatic

injury and failure, some ending in transplantation,<sup>6–8</sup> were recently reported and led to temporary suspension, followed in January 2021 by restricted use.<sup>9</sup>

We add further insights and details regarding a case report (with an image of the explanted liver) that was followed to the European Medicines Agency (EMA) and contributed to the final recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) that led to a restricted use of UPA.<sup>9,10</sup> Recently, the hypothetical hepatic toxicological mechanisms of UPA were also fully reviewed.<sup>7</sup>

## 2 | CASE REPORT

The present case report describes a 55-year-old woman who was diagnosed with acute liver injury 3 days after completing her first course of treatment with UPA (Esmya® 5 mg/day orally) for uterine fibroids that had caused persistent bleeding (treatment duration 109 days). She began treatment with UPA on 11 July 2014, and fatigue, asthenia, appetite changes (such as anorexia), dizziness and postprandial fullness occurred approximately 1 week later. On her own initiative, the patient consulted the drug information leaflet and noticed that these symptoms were reported therein. Saliva with a metallic flavour, intense halitosis, flatulence, changes in the smell of urine, and increased weight and breast size accompanied by pain were also described. Due to sleep disturbances, an herbal product (Sleep & Go®) containing lemon balm

(*Melissa officinalis* L., 500 mg/2 tablets), eschscholzia (*Eschscholzia californica* Cham., 500 mg/2 tablets), hops (*Humulus lupulus* L., 125 mg/2 tablets) and passion flower (*Passiflora incarnata* L., 150 mg/2 tablets) was taken twice but then discontinued for lack of efficacy. In October 2014, the patient began her fourth month of treatment, but due to dysuria and pollakiuria following a urinary tract infection by *Klebsiella pneumoniae*, cefuroxime (1500 mg, 12 h/12 h; 3 days) was taken just before the diagnosis of acute liver injury. The patient was hospitalized on 27 October 2014 due to extreme asthenia in the context of what was probably an acute toxic cholestatic injury and marked cytolysis, as evidenced by the levels of total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST) and lactate dehydrogenase (LDH) presented in Table 1, without coagulative alterations. Her clinical status worsened day by day. Abdominal ultrasound showed a

TABLE 1 Chronological overview of the case report

10 July, 2014	Beginning of the treatment for uterine fibroids
~20 July	Anorexia, asthenia, dizziness and postprandial fullness, without jaundice
~30 July	Saliva with metallic flavour, intense halitosis, flatulence, changes in the smell of urine, and increased weight and breast size accompanied by pain
August–September	Begun herbal product (Sleep & Go®) due to sleep disturbances, but immediate discontinuance due to absence of success
11 October	Beginning of the 4th month of treatment
21 October	Dysuria and micturition, <i>Klebsiella pneumoniae</i> in urine treated with cefuroxime (1500 mg, 12 h/12 h; 3 days)
27 October	Hospitalized due to extreme asthenia and acute liver injury AST 1443 U/L, ALT 1920 U/L, Total bilirubin 1.4 mg/dL, LDH 796 U/L, ALP 124 U/L
3 November	AST 1555 U/L, ALT 2211.6 U/L, Total bilirubin 1.5 mg/dL, LDH 719 U/L, GGT 97 U/L Values worsened day after day During hospitalization, the hepatoprotective drug <i>N</i> -acetylcysteine was administered along with prednisolone (maximum dose of 40 mg)
27 November	Abdominal ultrasound echography showed a liver with normal dimensions, but structure slightly hyperechogenic, probable related with the steatotic infiltration with some liver microcysts
1 December	Platelets count $98 \times 10^9/L$ (reference 150–450 $\times 10^9/L$ ) GGT 108 U/L, ALP 143 U/L, Total bilirubin 13.12 mg/dl, LDH 826 U/L
12 December	Successful liver transplantation
12 December	Liver macroscopic description - smooth greenish grey capsular surface with diminished consistency. The section surface exhibited a vaguely nodular appearance, greenish brown in colour and with hemorrhagic stippling. Hilum and suprahepatic vessels revealed no changes  Liver microscopy description - liver parenchyma with extensive areas of confluent necrosis, submassive, apparently centred on zone 3, along with others without evident zonation. There was a formation of centrilobular necrosis bridges and moderate mixed infiltrate without evident of eosinophils. Focal hepatocellular ballooning, focal areas of haemorrhage, focal parenchymal cholestasis, marked ductal proliferation and regenerative changes  Diagnosis - acute hepatocellular lesion, with confluent submassive necrosis, with no possible etiological clarification. Possible toxic injury was not excluded.

Abbreviations: AST, aspartate aminotransferase (reference 12–78 U/L); ALT, alanine aminotransferase (reference <34 U/L); total bilirubin reference <1.0 mg/dl; ALP, alkaline phosphatase (reference 45–129 U/L); LDH, lactate dehydrogenase (reference 208–378 U/L); GGT, gamma-glutamyl transferase (reference <38 U/L).

steatotic liver with some liver microcysts on admission. During hospitalization, the hepatoprotective drug *N*-acetylcysteine was administered along with prednisolone (maximum dose of 40 mg), but there was no apparent improvement in laboratory measurements. Liver transplantation was performed on 12 December 2014, approximately 6 weeks after UPA discontinuation. Figure 1 presents a macroscopic view of the explanted liver. A full description of the macroscopic and microscopic data is compiled in Table 1, the focal parenchymal cholestasis being particularly evident.

Notably, the patient had no history of abusing alcohol or other psychoactive substances, and she was negative for viral hepatitis caused by hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis E virus (HEV). Autoimmune hepatitis was excluded as a plausible aetiology because autoimmune anti-nuclear antibodies (ANAs), anti-double stranded DNA (anti-dsDNA) antibodies, anti-liver–kidney microsomal (anti-LKM) antibodies, anti-mitochondrial antibodies (AMAs), anti-smooth muscle antibodies (ASMAs) and c-anti-neutrophil cytoplasmic antibodies (ANCAs) were all negative. The patient's serological IgG positivity and IgM negativity for hepatitis A virus (HAV) were compatible with her history of hepatitis at 18 years of age. The serological tests for cytomegalovirus (CMV), Epstein–Barr virus (EBV), human immunodeficiency virus (HIV) I and II and herpesviruses were also negative. Ceruloplasmin and  $\alpha_1$ -antitrypsin showed no alterations.



**FIGURE 1** Macroscopic pathological examination of the explanted liver. A smooth greenish grey capsular surface with diminished consistency was evident. The section surface exhibited a vaguely nodular appearance, greenish brown in colour and with haemorrhagic stippling

### 3 | DISCUSSION

This case report suggests that UPA can cause liver failure. The reaction was classified as probable by the Portuguese National Authority of Medicines and Health Products (INFARMED) because it ‘occurred with an acceptable temporal relationship and the causal link with concomitant diseases or the administration of other drugs was considered unlikely’. This case was reported to the EMA via the Portuguese Pharmacovigilance System and has contributed to the final recommendations of PRAC.<sup>9–11</sup> The chronological, clinical and histological characteristics of acute hepatocellular injury followed by liver failure were compatible DILI<sup>12</sup> and consistent with UPA as a possible trigger. Among the causality assessment methods used for the diagnosis of DILI and herb-induced liver injury (HILI), Roussel Uclaf Causality Assessment Method (RUCAM) is one of the most widely used for individual cases and prospective and retrospective studies worldwide.<sup>13,14</sup> RUCAM attributes scores to individual key items, providing final quantitative gradings of causality of liver injury in 5 different categories (ranging from <24% being unlikely to >95% being definite) for each suspect drug/herb in a case report. In this case, RUCAM was scored as unlikely. In a very interesting study, Kang et al.<sup>15</sup> graded the five severe cases as probable likelihood and the remaining (one of which described in this case report) four cases to have a severity grade 2 and 3 (moderate and moderate to severe) and a RUCAM causality category of possible ( $n = 2$ ) or probable ( $n = 2$ ).

An exclusion diagnosis was performed for other causes of hepatic toxicity. The short courses of cefuroxime (second-generation cephalosporin) and of the herbal product (Sleep & Go<sup>®</sup>) were not considered plausible factors for DILI. Nevertheless, it should be highlighted that very few case reports have implicated cefuroxime as a cause of DILI and cholestasis, but those were calimed to be related to longer therapeutics.<sup>16,17</sup> Moreover, the patient's past clinical record showed no known relevant pathological history, and her case of acute viral hepatitis A at 18 years of age ended in full recovery. Indeed, in an analytical clinical evaluation performed approximately 1 year before her liver failure (i.e., in November 2013), the patient's liver function was perfectly normal, and approximately 1 month before she started treatment with UPA, her serum and urine biochemical tests were also normal, including protein electrophoresis, although transaminases were not evaluated. Similar conclusions were reported by Meunier et al.<sup>6</sup> The authors presented a very high-quality case report of a 58-year-old woman presenting

with acute hepatocellular injury complicated by subfulminant liver failure (with encephalopathy occurring approximately 2 weeks after the onset of jaundice), necessitating emergency liver transplantation.

Recently, the mechanisms (if any) involved in UPA as a DILI trigger are being attentively reviewed<sup>7,18–20</sup> but very far from being clearly understood. They are probably of an idiosyncratic nature, but they can also be dose dependent and related to the formation of reactive metabolites at the hepatic level, accumulation of UPA and/or its metabolites due to their long half-life and high lipophilicity, inhibition of liver transporters, and previous cirrhosis caused by alcohol abuse or chronic viral infection, which may predispose patients to cholestatic disease that decreases biliary excretion.<sup>7,19–23</sup>

The evolution of the patient's condition after transplant has been clinically acceptable, albeit with squeals as consequence of disease and adverse effects of treatments, and the patient has returned to professional activity. Due to DILI-related uncertainties, UPA prescriptions were reduced in the European Union and in several other countries. This case report suggests that liver function should be carefully monitored during the therapy with this drug and that further studies are needed to remove potential confounding factors that may predispose patients to DILI after UPA treatment.

## COMPLIANCE WITH ETHICAL STANDARDS

All procedures were performed according to the ethical and legal standards of the institution and the patient gave written informed consent to participate and consent for scientific publication.

## AUTHOR CONTRIBUTIONS

Both authors conceptualized the study. R.J. Dinis-Oliveira did the data curation, formal analysis, and writing the original draft, and both authors reviewed and edited the final version of the manuscript.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. No writing assistance was used in the production of this manuscript.

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