Liver injury and ulipristal acetate: an overstated tragedy?

Uterine fibroids are the most commonly encountered female pelvic tumors and the most frequent indication for hysterectomy (1) and associated with mortality rates of 0.02% to 0.17% and morbidity rates of 5.4% to 7.9%. Even myomectomy is not free of complications and the presence of myometrial scarring often requires caesarean section when giving birth.

Although alternative treatments like magnetic resonance-guided focused ultrasound and uterine artery embolization are associated with various advantages and disadvantages compared to surgery, there is a need for medical therapy to postpone surgical interventions or avoid surgery altogether in women wishing to do so. Gonadotropin-releasing hormone agonists are effective in reducing bleeding and fibroid size, but their use is limited to 3 to 6 months due to estrogen suppression, with its subsequent menopause-like symptoms.

Ulipristal acetate (UPA) reduces uterine bleeding, fibroid size, and uterine volume. Indeed, long-term intermittent treatment courses have proved effective, while maintaining estradiol values at mid-follicular phase levels (1–3). Therapeutic doses of 5 mg UPA (Esmya, Gedeon Richter PLC) were first authorized in the European Union on February 23, 2012. Post-marketing exposure to Esmya is estimated to be more than 765,000 patients so far, during which time some sporadic cases of liver injury and hepatic failure have been reported.

The European Medicines Agency announced temporary restrictive measures in February 2018, as five cases of drug-induced liver injury (DILI), four of which ended in liver transplantation, were potentially linked to Esmya administration. The Pharmacovigilance Risk Assessment Committee (PRAC) subsequently made temporary recommendations advising physicians not to take on new patients or initiate new treatment courses. In May 2018, the status of UPA as a potential DILI-inducing agent was neither confirmed nor fully ruled out, and the PRAC made recommendations to minimize the risks of liver injury, allowing patients to resume treatment.

Could We Have Anticipated these Cases of Liver Toxicity? What Is DILI?

DILI accounts for $<1\%$ of cases of acute liver injury seen by gastroenterologists but is the most common cause of acute liver failure in the U.S. and Europe, with an annual incidence of around 14-19 per 100,000 inhabitants. DILI typically involves a clinical diagnosis of exclusion, and management includes immediate cessation of the offending drug, with supportive therapy.

Historically, DILI is divided into intrinsic or idiosyncratic forms:

Intrinsic DILI: hepatotoxicity with potential to affect all individuals to varying degrees. Reaction typically stereotypic and dose-dependent (e.g. acetaminophen [paracetamol]).

Idiosyncratic DILI: hepatotoxicity affecting only rare susceptible individuals. Reaction less dose-dependent and more varied in latency, presentation, and course.

These idiosyncratic and diverse disease presentations of DILI make research particularly challenging, as the mechanistic understanding of this condition is still limited.

Criteria for Evaluation of Abnormal Liver Safety Values

Based on Hy's law (FDA DILI guidelines, July 2009), indicators of DILI are alanine aminotransferase (ALT) or aspartate transaminase (AST) over 3 times the upper limit of normal (ULN) (signs of liver cell injury) and total bilirubin in excess of 2 times ULN. Hy's law best anticipates the risk of mortality/liver transplantation (4, 5). Elevations of ALT to 3x ULN and alkaline phosphatase (ALP) to 2 times ULN are rare (0.5%) in populations without underlying liver disease and can therefore be regarded as safety signals (4, 5). Bilirubin was itself considered a liver function test to indicate functionality, but also exclude initial signs of cholestasis by looking at ALT $\times$ ULN/ALP $\times$ ULN <2. Furthermore, if a drug is stopped in a timely manner (i.e. as soon as possible), there is normally rapid resolution of the DILI in case of most medications potentially causing liver injury.

Data from Clinical Trials

Liver data were reviewed in all UPA clinical trials during the development program, in order to assess liver safety.

Phase I clinical trials. In the reviewed phase I clinical trials involving multiple daily oral doses, 160 subjects were exposed to 2.5, 5, 10, 20, or 50 mg UPA a day. Repeated daily administration up to 10-fold the marketed dose (5 mg) and as many as 10 days of exposure to UPA did not result in any change in ALT, AST, ALP, bilirubin, or gamma-glutamyl transferase (GGT) levels in these individuals.

Phase II clinical trials. In phase II clinical trials, 152 subjects were exposed to 2.5, 5, 10, or 20 mg daily. Relevant exclusion criteria at screening in phase II (and III) clinical trials included ALT, AST, ALP, GGT and bilirubin more than 2 times ULN, or alcohol abuse. In these trials with daily doses up to 4-fold the marketed dose (5 mg) for 12 weeks, values of ALT/AST greater than 2 times ULN or total bilirubin greater than 1.5 times ULN were never observed.

Phase III clinical trials. In phase III clinical trials, 1,556 subjects were exposed to 5 and 10 mg UPA daily for one or multiple (up to eight) 3-month treatment courses. Exclusion criteria were the same as for phase II trials. It is important to note that while ALT is liver-specific, elevations in AST may also be associated with damage to skeletal or cardiac muscle, or conditions such as myocardial infarction and rhabdomyolysis. ALT values above 3 times ULN were observed in 8 subjects across all phase III trials after administration of at least one dose of UPA (Table 1).

These phase III trials were subdivided into a series of further investigations known as the PEARL studies, evaluating the safety and efficacy of UPA use. In the PEARL I

TABLE 1

Elevated liver tests during phase III clinical trials.

Laboratory value	5 mg UPA (N = 678), n (%)	10 mg UPA (N = 878), n (%)
ALT or AST > 3× ULN	0	8 (0.9)
ALT or AST > 5× ULN	1 (0.1)[a]	2 (0.2)
ALT or AST > 10× ULN	0	0

Note: Subjects are counted only once in the highest elevation category. ALT = alanine aminotransferase; AST = aspartate transaminase; ULN = upper limit of normal; UPA = ulipristal acetate.

[a] At screening: as liver enzymes were normalized at baseline, the patient was included in the study and did not show any increase in liver enzymes during the trial.

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study, 3 subjects (10 mg UPA group) had ALT levels greater than 3 times ULN. These values had returned to normal by the 6-month follow-up visit. In the PEARL II and PEARL III extension studies, no subjects showed ALT above 3 times ULN in any group at any visit. In PEARL II, no one in the leuprorelin group had ALT levels above 3 times ULN. In PEARL III, one subject given 10 mg UPA showed ALT values more than 3 times ULN. She had drunk 500 mL of red wine 48 hours prior to the visit. Two retests (one and two weeks later) showed a constant decrease in transaminase values under treatment.

In the PEARL IV study, 4 subjects had ALT levels over 3 times ULN. The first subject (5 mg UPA) showed ALT greater than 3 times ULN only at screening. By baseline, these values had returned to normal and, very importantly, remained there throughout the study. The second subject (10 mg UPA) showed high ALT values at screening, and at baseline reached 4.3 times ULN, with AST 1.1 times ULN and GGT 1.8 times ULN. Ten days later, she was diagnosed with cholelithiasis. Two months later, all liver tests were back within normal range and a scheduled cholecystectomy was performed. However, by the end of the first treatment course, ALT levels had again increased to 4 times ULN, with AST 2.1 times x ULN, direct bilirubin 1.7 times ULN and GGT 1.9x ULN. Approximately one month later, the subject underwent emergency surgery due to obstruction of the small intestine and her liver test results remained within normal range up to the end of the study. She completed all four treatment courses. The third subject (10 mg UPA) showed ALT levels of 1.7 times ULN with AST 1.1 times ULN by the end of the first treatment course, and ALT 3.9 times ULN with AST 2.3 times ULN one month later (unscheduled visit between two treatment courses). When she was due to start her second treatment course, the subject decided to discontinue participation in the study. The fourth subject (10 mg UPA) showed elevated GGT (1.8 times ULN) with ALP 1.1 times ULN at screening, and GGT 2.4 times ULN with ALP 1.2 times ULN at baseline. In the second month of treatment, she reached values of ALT 3.5 times ULN, with AST 1.9 times ULN and GGT 12.4 times ULN, followed by a decrease in levels during subsequent unscheduled visits. After the last laboratory results, the subject decided to cease participation in the study.

In conclusion, as seen in Table 1, eight women taking 10 mg UPA had ALT or AST levels above 3 ULN, and two patients also taking 10 mg UPA had ALT or AST values above 5 ULN. No one taking 5 mg UPA had ALT or AST levels above 3 ULN during treatment.

Commentary

UPA is not a member of any of the therapeutic categories of drugs associated with an increased risk of DILI and does not share any structural similarities with the compounds listed by the Drug-Induced Liver Injury Network as chemical subgroups/types of molecules known to pose a greater risk (4), notably the top 100. Drugs causing most concern include amoxicillin-clavulanic combinations, anti-tuberculous agents, ketolides, macrolides, triazole derivatives, non-nucleoside reverse transcriptase inhibitors, protein kinase inhibitors, nonsteroidal anti-inflammatory drugs-type drugs of the phenylacetic acid class and interferons.

Unfortunately, some individuals exposed to a therapeutic dose of UPA may develop idiosyncratic DILI with potentially serious clinical outcomes, but no biomarkers are currently available to identify susceptible patients prior to drug treatment.

In the course of post-marketing, sporadic cases of liver injury and hepatic failure were reported with Esmya. All liver data from the clinical trials were reviewed and no patients taking 5 mg UPA (the authorized therapeutic dose) showed any anomalies of liver enzymes. Indeed, phase I and II clinical trials did not find any cause for concern in relation to Esmya use. With regard to phase III trials, detailed review showed isolated transient increases in several liver function tests before, during and/or after treatment in very few patients. However, there are no findings raising particular concerns with respect to UPA.

We would therefore never suspect liver toxicity on the basis of data from the clinical trials. UPA was very well tolerated and there were no safety signals related to liver injury during clinical development, even with up to eight intermittent courses of UPA.

In conclusion, considering the five acute liver failures that occurred among 765,000 patients and the absence of signs of liver injury reported in the clinical trials, one could postulate that this is a very rare idiosyncratic event of DILI. There is no doubt that excluding patients with liver anomalies or disorders at screening (as was done during the clinical trials) and checking liver enzymes during treatment courses will minimize the risks further.

The benefits of UPA for fibroid management remain clear. Indeed, there is currently no medical alternative to surgery for treatment of moderate and severe fibroid-related symptoms.

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