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COMMENTARY

Liver Injury Associated with the Selective Progesterone Modulator Ulipristal

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In most medical schools, the story of thalidomide has been told at some point, its use during pregnancy in Europe leading to birth defects in thousands of exposed children and how the US Food and Drug Administration (FDA) prevented its entry into the US market [1]. Approximately 40 years later in 1997, the FDA approved troglitazone, an antidiabetic drug, in the USA. In the middle of the same year, it was also marketed in the UK. However, after reports of liver failure, it was removed from the British market in December 1997 [2], but not from the US market. In 1998, a 55-year-old woman died of acute liver failure caused by troglitazone as a participant in a National Institutes of Health-sponsored study, but closely monitored by physicians [3]. However, it was not until the year 2000 that the FDA removed the drug from the market after reports of many deaths due to acute liver failure [4]. Up to 2003, over 200 cases of fatal hepatic reactions due to acute liver failure suspected to be related to troglitazone use were reported to VigiBase, the World Health Organization global database of individual case safety reports, the vast majority of which were from the USA [5]. Thus, both a restrictive and a liberal strategy by the FDA in terms of drug safety is illustrated by these examples above.

Invited editorial on: "An evaluation of postmarketing reports of serious idiosyncratic liver injury associated with ulipristal acetat for the treatment of uterine fibroids" by Kang et al and "Liver Injury with Ulipristal Acetate: Exploring the Underlying Pharmacological Basis" by Gatti et al.

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It is well known that a majority of adverse events including rare events are identified during the post-marketing phase of a drug when it is used in the wider population. Drug-induced liver injury (DILI) is one of the most common causes of withdrawal from the market of otherwise promising drugs [6]. In this issue of *Drug Safety,* two studies on DILI related to the use of a newly marketed selective progesterone receptor modulator, ulipristal acetate (UPA), illustrate this problem.

In the first study, Kang et al. presented an evaluation of the FDA reports of suspected DILI associated with UPA [7]. In the second study, Gatti et al. [8] analysed the pharmacological properties of UPA to explore the pathophysiology of DILI due to this drug.

1 Indications, Mechanism of Action and History of Drug-Induced Liver Injury Due to Ulipristal Acetate

In 2012, UPA 5 mg/day was approved by the European Medicines Agency (EMA) for the treatment of moderate or severe symptoms of uterine fibroids such as heavy vaginal bleeding and/or pelvic pain as an alternative to surgery (hysterectomy) [9]. Although the exact mechanism of action is not fully known, the agent seems to antagonise the progesterone receptors without influencing the estrogen effects in endometrial tissue [10]. In the phase I–II clinical trials of UPA, no liver-related adverse effects were observed [11, 12]. In the phase III trials of UPA, the proportion of patients with alanine aminotransferase levels more than three times the upper limit of normal was similar in patients receiving the active treatment to those receiving placebo [13]. Over 1800 subjects were exposed to UPA in the phase I–III trials prior to approval, which is a small cohort for an adverse effect as rare as idiosyncratic DILI to appear. There is a paucity of evidence on the proportion of patients treated with hepatotoxic drugs who develop DILI. In one population-based

study in Iceland, DILI occurred in 1 of 2350 users of amoxicillin-clavulanate [14]. Thus, the clinical trials with UPA were obviously underpowered to detect rare adverse effects such as DILI.

According to a report from the EMA in 2018, 765,000 women had been cumulatively exposed to UPA [15]. At that time, 105 cases of suspected liver injury (33 serious and 72 non-serious cases) had been reported [15]. Overall, four cases were reported with acute liver failure requiring liver transplantation. Based on available data at the time, the EMA concluded that the benefit-risk balance of UPA remained favourable. Furthermore, the proposed risk minimisation activities by the market authorisation holder of UPA were considered to adequately address the concerns regarding the potential liver toxicity and new patients were approved for treatment with the drug [15]. Further publications supported this conclusion [16, 17] with one article concluding that 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 sub-groups/types of molecules known to pose a greater risk [of DILI]" [17]. Thus, despite frequent reporting of liver injury including some serious reports, the hepatotoxicity of UPA was neither confirmed nor ruled out [15]. On 13 March, 2020, the EMA decided to temporarily suspend the use of UPA for the treatment of uterine fibroids and recommended that any ongoing treatment should be immediately stopped [18]. This was following the reports of more serious cases of hepatotoxicity including another case of serious liver injury resulting in liver transplantation.

2 Evaluation of Post-Marketing Reports

Although the spontaneous reporting of suspected serious DILI cases was assessed by the EMA [15], detailed analysis of post-marketing reports was lacking until the study by Kang et al. in this issue of *Drug Safety* [7]. The authors reviewed nine cases (median age 48 years) of suspected DILI that were spontaneouly reported to the FDA, five of whom underwent liver transplantation with successful outcomes except one case who died of septic complications post-transplant. The clinical and biochemical phenotypes of the liver injury were rather similar with acute hepatocellular injury and histological features of submassive hepatocellular necrosis. In 77% of the patients (7/9 patients), the time to onset for symptoms of liver injury was within 3 months from treatment initiation. This is important as UPA was approved by the EMA for a single 3-month course of treatment [10]. Furthermore, none of the patients had evidence or a history of chronic liver disease. Thus, assuming that UPA should only be avoided in patients with chronic liver disease would probably provide a false sense of security [16, 17]. The aim of the study to "perform a comprehensive analysis" was fulfilled and has increased the knowledge in the field of DILI of important safety aspects of newly marketed drugs that can occur in the post-marketing phase. This type of research on the safety analysis of drugs is very important to throw light on the adverse effects of newly marketed drugs. Ulipristal acetate was never approved for the treatment of uterine fibroids in the USA and probably never will. Although the drug might have been able to improve the quality of lives of the patients who missed the opportunity to try this drug, the fact that it was never marketed probably saved many lives of otherwise healthy young and middle-aged women.

3 Mechanisms by Which Ulipristal Acetate Could Cause Hepatotoxicity

The description and analysis of clinically apparent case reports of liver injury associated with UPA show that it is convincingly related to this agent, although a re-challenge case has not been reported [7, 19]. What could be the underlying mechanism? Administration at a relatively low daily dose (5 mg) would argue against a hepatotoxic potential. The majority of drugs leading to idiosyncratic DILI are given in a daily dose of > 50 mg per day [20]. However, drugs with a daily dose of < 10 mg caused 9% of drug-induced jaundice in Sweden [20, 21]. Reactive metabolites created by the hepatic metabolism of drugs are considered to play an important role in the pathophysiology of DILI. Drugs heavily metabolised within the liver were found to be more likely to be associated with hepatotoxicity [22]. Ulipristal acetate and its metabolites are eliminated slowly with a half-life of 35–45 h but in clinical studies there was no unexpected accumulation of maximum concentration and area under the curve and accumulation of repeated dosing was around two-fold [15]. The main route of elimination is through cytochrome P450 in the liver and through bile and faeces and less than 10% of the drug is excreted in urine. However, only traces of a reactive UPA metabolite was identified in human faeces. Thus, there is not much argument in favour of reactive UPA metabolites increasing the risk of hepatotoxicity [15]. The lipophilicity is relatively high for UPA (LogP 4.45), which has been identified as a risk factor for DILI [23].

The second study on UPA by Gatti et al. [8] in this issue of *Drug Safety* is an important study that explored the physiochemical and pharmacokinetic features potentially involved in DILI and compared UPA with mifepristone and leuprolide. A significantly higher proportion of liver disorders was reported for UPA than for mifepristone and leuprolide including autoimmune hepatitis. Unfortunately, no case

reports of autoimmune hepatitis have been reported, thus it is still unclear if UPA does lead to autoimmune hepatitis.

Despite similar physiochemical features for mifepristone and UPA, the former was significantly less likely to cause DILI [8]. Mifepristone fulfilled the "rule-of-two", given in a high daily dose and having a high lipophilicity, whereas UPA had a low daily dose. Although the authors suggest that DILI due to UPA might be partly explained by high lipophilicity, extensive hepatic metabolism and a long half-life, the data to provide firm evidence for this are very scarce. To make a long study short: the pathogenesis behind DILI due to UPA is still unclear.

Recently, on 4 September, 2020, the EMA's Pharmacovigilance Risk Assessment Committee, which is responsible for assessing all aspects of the risk management of medicines for human use at the EMA, confirmed that 5 mg of UPA can cause liver injury, including the need for liver transplantation. The Pharmacovigilance Risk Assessment Committee therefore recommended revocation of the marketing authorisation of this medicine (https://www.ema.europa.eu/en/news/prac-recommends-revoking-marketing-authorisation-ulipristal-acetate-uterine-fibroids).

Taken together, there are several interesting points highlighted by the story of UPA.

- A summary report by the EMA of more than 100 cases of liver injury post-marketing with four liver transplants after short-term treatment could neither confirm nor rule out DILI due to UPA and treatment with UPA continued for 2 more years, leading to more hepatic reactions until it was suspended.
- Physiochemical and pharmacokinetic properties of UPA did not suggest an apparent risk for DILI, which should stimulate further research into the potential underlying mechanism of drug properties in general to reduce the risk of DILI in the future.
- Well-characterised post-marketing cases of DILI must be taken seriously.
- As it was not possible to identify which patients were most at risk or to identify measures that could reduce the risk, the Pharmacovigilance Risk Assessment Committee concluded that the risks of these medicines outweighed their benefits and that they should not be marketed in the European Union.
- Studies quantifying the risk for DILI post-marketing are largely lacking and should be encouraged to better evaluate the benefit-risk balance of a given drug.

Declarations

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