

Survey of Portuguese gynaecologists regarding drug-induced liver injury associates with ulipristal acetate in the treatment of uterine fibroids

Inquérito aos ginecologistas portugueses sobre lesão hepática induzida por drogas associada ao acetato ulipristal no tratamento de miomas uterinos

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Abstract

Introduction: Ulipristal acetate (UPA) was introduced in clinical practice for the treatment of uterine fibroids in February 2012. During the post-marketing exposure, there were reports of liver injury and the European Medicine Agency recommended monitoring of liver enzymes for safety reasons.

Objectives: The aim of this survey was to gather information about Portuguese gynaecologists' experience with UPA regarding liver function and other complications related to UPA use.

Material and methods: The study consisted of a cross-section survey among members of the Portuguese Society of Gynaecology between April and May 2018. The responders used an online platform to answer a survey that focused on safety and specific alterations in laboratory analyses of liver function considering treatment with UPA since January 2018.

Results: In the period considered in this survey, 199 women were treated with UPA by the responders. Monitoring of liver function was performed in 93 women and alterations in liver function laboratory tests were reported in five cases (2.5%). In two of these cases, the past medical history was associated with liver diseases, namely alcoholic, infectious and autoimmune. The clinical course was favourable in all cases.

Conclusions: Despite temporary UPA temporary suspension, this survey reinforced the need of clinical database for UPA safety monitoring, particularly regarding the possible application in selected clinical cases.

Keyword: Uterine fibroid; Leiomyoma; Ulipristal acetate; Drug-induced liver injury.

INTRODUCTION

Ulipristal acetate (UPA) has been available in Europe since 2012 for the treatment of moderate to severe symptoms of uterine fibroids in reproductive age women. According to data from the European Medicines Agency (EMA), it is estimated that more than 765,000 women have been treated up to February 2018¹.

In February 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA issued a

temporary recommendation advising that new courses of treatment with UPA should not be initiated. The local regulatory entity also transmitted this and further

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recommended monitoring the liver function of patients currently under treatment. UPA should be suspended if transaminases levels exceed twice the maximum limit².

The Portuguese Society of Gynaecology decided to survey its members' experience with UPA using an on-line questionnaire, in order to contribute to better knowledge about its use in Portuguese women, particularly regarding liver function.

METHODS

This cross-sectional study was conducted among members of the Portuguese Society of Gynaecology between April and May 2018. All members of the Portuguese Society of Gynaecology have allowed access to their e-mail contact for Society surveys. The Board of the Portuguese Society of Gynaecology gave permission for the application of the questionnaire.

Ethical approval was not necessary as the members of the Portuguese Society of Gynaecology were freely invited to complete the questionnaire and gave their consent to access the email address.

The entire online database represents a total of 783 members that receive the survey, residents and specialists in gynaecology, working in public and private practice in Portugal. The questionnaire was administered anonymously using a link received by e-mail to an online survey platform.

The study instrument had twenty-two questions and was restricted to questions about the prescription of UPA since January 2018, either for the continuation or beginning of treatment.

The first part consisted of questions assessing the number of patients treated and the previously available assessment of hepatic function, with particular emphasis on transaminases, aspartate transaminase (AST) and alanine transaminase (ALT), gamma-glutamyltransferase (GGT), bilirubin (BRB) and alkaline phosphatase (ALP).

The second part addressed the assessment of hepatic function after the beginning of treatment. The survey inquired about clinical and laboratory findings, namely increase in levels of AST, ALT, BRB of twice the normal upper limit and three times the normal upper limit. The study of other laboratory tests was also requested as well as prior hepatic diseases of other aetiologies.

The third part assessed the need to suspend treatment, the clinical course of hepatic dysfunction and the subsequent treatment of uterine fibroids.

RESULTS

Sixty-two gynaecologists answered the survey, a response rate ranged 7,9%. Considering the responders, 48 had prescribed UPA for new or continued treatment after 1st January 2018. During this period, 199 women were treated.

The physicians who prescribed the drug reported that liver function had been assessed before treatment in 19 cases. In three of these cases alterations were detected in liver function (elevation of transaminases in two cases and GGT in one case) prior to treatment.

According to the responders, the evaluation of hepatic function was performed in 96 women after UPA start and in 63 the assessment of liver function included not only transaminases but also bilirubin.

In five cases, described in Table I, were detected elevation of transaminases; in three cases the blood concentration level did not double but in two cases there was an increase greater than threefold.

In the cases in which hepatic function was altered after treatment, complementary studies were performed in three women and hypoalbuminemia and abnormalities in hepatic ultrasound were detected.

Considering the five women diagnosed with hepatic impairment: there was a history of liver disease in two cases (alcoholic, infectious liver disease and autoimmune hepatitis); treatment with UPA was suspended in three of these patients (and one patient continued medical treatment with a hormonal contraceptive); other two cases continued treatment without other adverse events.

In all cases, a favourable evolution of liver function abnormalities diagnosed during monitoring was described.

DISCUSSION

The incidence of drug-induced liver injury (DILI) is between 10 and 15 per 10000 to 100000 exposed³. DILI accounts for 10% of cases of acute hepatitis and is the most frequent cause of acute liver failure in the United States⁴. This is the first reason to withdraw drugs from the market. Hepatic toxicity may not be detected in clinical trials prior to drug approval because many trials include fewer than 3000 participants and adverse events with an incidence lower than 1 in 10000 are rare⁵.

More than 1000 products, medicines and herbal products have been associated with liver toxicity⁶.

TABLE I. CASES OF UPA USE FOR UTERINE FIBROIDS WITH ALTERATION IN LIVER FUNCTION.

Case	Personal history	Liver function		UPA	Follow-up
		Before treatment	After treatment	Suspension	
1	Autoimmune hepatitis	↑ GGT	↑ ALT or AST (increased > 3x)	Yes	Favourable
2	Irrelevant	↑ ALT or AST	↑ ALT or AST (increased < 2x)	No	Favourable
3	Irrelevant	Normal	↑ ALT or AST (increased < 2x)	No	Favourable
4	Irrelevant	Not performed	↑ ALT or AST (increased < 2x)	Yes	Favourable (medical treatment)
5	Alcoholic Infectious hepatitis	↑ ALT or AST	↑ ALT or AST ↑ Bilirubin (increased > 3x)	Yes	Favourable

↑: increase; x: times; aspartate transaminase (AST); alanine transaminase (ALT); gamma-glutamyltransferase (GGT).

Many of these are currently used in clinical practice, particularly antibiotics such as amoxicillin/clavulanic acid and erythromycin; antifungals such as imidazole, fluconazole and itraconazole; antithyroid drugs such as propylthiouracil and methimazole; and also oral hormonal contraceptives, which are among the most often prescribed by gynaecologists. The mechanisms of toxic hepatitis by drugs are not yet fully understood and include hepatocellular and extracellular mechanisms with lesion of bile duct epithelium³.

There are two main groups of reactions to drugs: direct liver damage and autoimmune response. The intrinsic or predictable reactions cause lesions that are reproducible and dose dependent. The injury may be due to the drug itself or to a metabolite. An example of this type of toxicity is that caused by paracetamol in high doses. Idiosyncratic reactions may be subdivided into hypersensitivity or immunoallergic or those that are metabolic/idiosyncratic. In these cases the response is variable and can occur at different times and in a minority of patients⁷.

UPA was marketed in Europe and in Portugal in 2012 and was previously tested in several pre-clinical animal studies and phase I, II and III trials⁸. Animal studies demonstrated no hepatic toxicity and no molecular similarities to compounds that have been associated with DILI⁸. It was in the post-marketing period that severe hepatic lesions were reported, however with a variable clinical pattern, namely onset of symptoms from within a few days to months after the first dose. The association with underlying chronic liver disease and absence

of complete information on concomitant medications and co-morbidities does not allow a cause-effect relationship to be established between the drug and these adverse events. However, as such an association cannot be completely ruled out, this justifies the recommendations focusing on the need for close monitoring before the onset and during the treatment with UPA⁹.

Potential confounders are pointed to this study, namely the voluntary participation of the society members. Several aspects of clinical data were not included as the aim was to describe clinical experience and liver function alterations related to treatment. This study can have potential bias, considering it is an observational study conducted by a scientific society to the members by e-mail. Besides this fact the unique source of clinical data is the doctor report. We also recognize a low response rate, but we aimed to analyse the clinical experience and the severity of adverse outcomes considering the liver function.

Our survey provided information about 199 patients who received UPA in Portugal. Of this group, 2.5% (five cases) presented elevated liver enzymes after onset of treatment, but in only 1% (two cases) with clinical relevance. It should be noted that in both cases there was a previous history of liver disease, what emphasizes that UPA should not be considered in patients with previous liver disease. All cases had a favourable evolution. In cases with mild elevation of transaminases, the continuation of UPA did not worsen laboratory data and no serious adverse effect were reported. More severe enzyme levels did not continued treatment.

UPA is an effective drug but the relationship between UPA and rare hepatic lesions led to temporary suspension in 2020¹⁰. In the future, the use of UPA will probably be limited to selected clinical sceneries, namely surgical contraindication, fibroid embolization and surgical fails¹¹. The results of this investigation reinforce the need for careful and systematic collection of the clinical data of women treated with UPA and strict monitoring of hepatic function according with authorities' recommendations of 2021. EMA restricted the use of UPA for intermittent treatment of moderate to severe symptoms of uterine fibroids in premenopausal women, when other options are not adequate or failed.

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CONFLICT OF INTERESTS AND FUNDING

The authors report no personal conflict of interests and ensure that only they had access to the results.

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ANEXO

INQUÉRITO SOBRE ACETATO DE ULIPRISTAL E FUNÇÃO HEPÁTICA

- 1) Quantas mulheres tratou com acetato de ulipristal no último ano?

- 2) Quantas mulheres dessas mulheres estão em tratamento desde Janeiro de 2018?

- 3) Existia alguma avaliação da função hepática pré-tratamento?
Não ☐ Sim ☐
- 4) A avaliação da função hepática apresentava alterações?
Não ☐ SIM ☐
Qual?
Transaminases ☐
GGT ☐
Bilirrubinas ☐
Fosfatase alcalina ☐
Outras ☐
- 5) A quantas mulheres foi feita uma avaliação hepática após o início do tratamento com doseamento das transaminases?

Houve algum caso de aumento das transaminases?
Não ☐ Sim ☐
Quantos casos _____
No caso de ter havido algum caso, os valores da TGP e ou da TGO foram: (responda a cada caso separadamente)
a) Até 2 vezes o valor máximo considerado normal no laboratório
_____ casos
b) Até 3 vezes o valor máximo considerado normal no laboratório
_____ casos
- 6) A quantas mulheres foi feita avaliação hepática com doseamento das bilirrubinas? _____
Houve algum caso de aumento das bilirrubinas?
Não ☐ Sim ☐
Quantos casos _____
No caso de ter havido algum caso, os valores das BRBs foram: (responda a cada caso separadamente)
- a) Até 2 vezes o valor máximo considerado normal no laboratório
_____ casos
- b) Até 3 vezes o valor máximo considerado normal no laboratório
_____ casos
- 7) Nos casos com alterações:
 - a) A doente fez uma avaliação adicional da função hepática?
Não ☐ Sim ☐
Qual (descreva as análises)?
Albumina ☐
Provas de coagulação ☐
Outras ☐
 - b) A doente tinha antecedentes de:
 - i) Hepatite tóxica de outra etiologia?
Não ☐ Sim ☐
Qual?
Alcoólica ☐
Consumo excessivo de analgésicos ☐
Produtos de ervanária e outros suplementos ☐
Químicos industriais ☐
Outros fármacos ☐
Especificar _____
 - ii) De hepatite de outra etiologia:
Não ☐ Sim ☐
Qual?
Infecciosa ☐
Auto-imune ☐
Outras ☐
 - c) Suspendeu o tratamento?
Não ☐ Sim ☐
 - d) Como foi a evolução do caso?
 - i) Favorável ☐
 - ii) Cronicidade ☐
 - iii) Transplante hepático ☐
- 8) Nos casos em que foi diagnosticada patologia hepática, qual foi a orientação clínica dos miomas uterinos
 - a) Tratamento expectante
 - b) Tratamento com estroprogestativo ou progestativo
 - c) Tratamento com análogos da GnRH
 - d) Miomectomia
 - f) Histerectomia