Is Ulipristal Acetate a Liver Toxic Biomolecule? 
Toxicity assessment of ulipristal acetate

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Progestrone is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. Its main functions are playing a key role in the development, differentiation, and normal functioning of female reproduction-related target tissues including the uterus (endometrium and myometrium), the ovary, and the mammary gland, as well as regulating the hypothalamic–pituitary–gonadal axis. Soon after the discovery of the progesterone receptor (PR) it was appreciated that the development of a PR antagonist would have a major therapeutic potential. Numerous related compounds have been synthesized exhibiting a spectrum of activity ranging from pure progesterone receptor antagonists (PA), to mixed agonists/antagonists. These latter compounds are also known as selective progesterone receptor modulators (SPRM), progesterone receptor modulators (PRM), mesoprogestins or partial agonist–antagonists. Ulipristal acetate is a SPRM used in Europe for preoperative treatment of moderate-to-severe symptoms of uterine leiomyomas in adult women of reproductive age [3]. This is a retrospective cohort study conducted in two medical units, Saint John Hospital and Egometacs Clinic, between January 2017-December 2018, on women treated with UPA (ulipristal acetate) for symptomatic uterine fibroids, in order to evaluate if there were any liver function changes after the treatment. In the mentioned period, 74 women were treated with UPA for symptomatic uterine myomas in the two units. After checking the records, 6 women were lost on follow up (only the first visit was recorded), 4 didn’t complete the treatment course and 7 had incomplete laboratory evaluation, either at the beginning or at the end of treatment. Finally, our cohort was comprised of 57 women, aged between 20 and 50 years old, treated with UPA for various conditions (myomas, abnormal bleeding pelvic pain etc.) during a period of 3 months, and adherence to treatment was 100%. We performed a paired T-test on the before and after values of the AST, ALT, GGT enzymes and total bilirubin levels, for our statistical analysis we used SPPS 20, and the charts were built using Microsoft Excel. There were no significant statistical differences between the before and after values of the variables measured in our study. In our study the paired T-test determined that there were no statistical significant differences between the liver function after Esmya administration. Although there was no evidence of hepatic impairment in the 3 months course of treatment, precautions as the one recommended by EMA, should be respected. Still, more studies are needed in order to rule out the potential harmful effect of UPA on the liver, taking into account detailed liver function evaluation and extended laboratory tests. Until then, the temporary safety measures issued by the European Medicines Agency, are to be respected. The measures include: no use of UPA for women with known liver conditions, careful monitoring of liver function monthly for the patients under treatment and at four weeks after, and immediate discontinuation and report of any adverse complaints.

Keywords: progesterone, ulipristal acetate, selective progesterone receptor modulators, leiomyoma

Progestrone is a hormone steroid that plays an essential role in humans and mammals due to its role in the menstrual cycle, pregnancy, and embryogenesis. It belongs to a group of steroid hormones called the progestogensand is considered the major steroid with progestogen activity in the human body due to its many functions [1]. It is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid [2]. Progesteron activity in the cells are mediated by a progesterone receptor (PR) discovered in 1970 by Sherman et al.. After that epochal discovery the therapeutic potential of PR antagonists was foreseen by many authors. Among PR antagonists and modulators, Ulipristal acetate is a SPRM used in Europe for preoperative treatment of moderate-to-severe symptoms of uterine leiomyomas in adult women of reproductive age. Like other SPRMs, UPA reduces menstrual bleeding and fibroid volume [3]. Ulipristal acetate (UPA) [9] (11beta)-(17) (acetyloxy)-11-(4-(dimethylamino)phenyl)-19-norpregn-4,9-diene-3,20-dione known as Esmya has a molecular weight of 475.629 g/mol, with 0 hydrogen bond donor count, and 5 hydrogen bond acceptor counts, with a topological polar surface area of 63.7 A², with a heavy atom count of 35, a defined atom stereocenter count of 0 and covalently-bonded unit count of 1 (scheme 1)[4]. Ulipristal Acetate is an orally bioavailable,acetate salt of ulipristal, a selective progesterone receptor modulator with anti-progesterone activity. Ulipristal binds to the progesterone receptor (PR), thereby inhibiting PR-mediated gene expression, and interfering with progesterone activity in the reproductive system [5,6]. As a result, this agent may suppress the growth of uterine leiomyomatisosis. The mechanisms responsible for these effects remain vastly unknown. Furthermore, by inhibiting or delaying ovulation and effecting endometrial tissue, ulipristal can be used as an emergency contraception [7,8]. UPA metabolism is liver dependent, excreted by feces and bile, and predominantly mediated by CYP3A4. Studies have shown no major interactions with CYP3A4 inhibitors and inducers, and no interactions with major drug transport proteins [9,10]. Also, progesterone is used as a contraceptive method highly efficient, before or after a pregnancy [11,12]. Antiprogestagens chemical compounds are part of different methods of abortion induction [13].

Recently (February 2018), Medicines & Healthcare products Regulatory Agency (MHRA) issued a warning...
concerning new temporary safety measures for Esmya (ulipristal acetate) following reports of serious liver injury in women using the medicine for uterine fibroids. In the letter, MHRA mentioned four reports of serious liver disease in women taking UPA for uterine fibroids, and recommended liver function check before the treatment initiation and monthly during the treatment in order to avoid liver insufficiency. [14]. Following the warning we decided to evaluate the liver function in women who received UPA for uterine fibroids, and to assess if there are significant changes after the treatment.

Experimental part
Material and methods
This is a retrospective cohort study conducted in two units, St John Hospital and Egometacs Clinic between January 2017–December 2018, on women treated with UPA for symptomatic uterine fibroids. Data were retrieved from the patients’ files and records. The inclusion criteria were: premenopausal women with symptomatic uterine fibroids (bleeding, infertility, pain) prior to surgery, or those who desired to preserve their fertility. All women were given 10 mg UPA daily for a three month course. At the treatment initiation, regular blood test were performed in order to assess the presence of anemia, as well as hepatic and renal functions. The same laboratory tests were performed at the end of the third month. Patients with liver function impairment, liver disease history and renal function impairment were excluded. We retained only the patients that completed the three months course, those that didn’t comply, were lost on follow up or needed surgery before the end of the course were excluded.

Statistical analysis
In order to evaluate liver function the following variables were measured: AST, ALT, GGT and total bilirubin. Their values were noted at the two moments - start and end of treatment. The outcomes followed were the significant changes that could indicate liver function impairment. The values were measured in international units per litre (UI/L) and mg/dL, and the normal values for our laboratory were 10-40 UI/L for AST, 10-50 UI/L for ALT, 10-50 UI/L for GGT and 0.2-1.2 mg/dL for total bilirubin. All the measurements were performed in a single laboratory, and the patients that were not tested in our laboratory were excluded in order to avoid any errors. The data was processed using SPPS 20. We performed a paired T-test on the before and after values of the AST, ALT, GGT enzymes and total bilirubin levels, for our statistical analysis we used SPPS 20, and the charts were built using Microsoft Excel.

Results and discussions
In the mentioned period, 74 women were treated with UPA for symptomatic uterine myomas in the two units. After checking the records, 6 women were lost on follow up (only the first visit was recorded), 4 didn’t complete the treatment course, and 7 had incomplete laboratory evaluation either at the beginning or at the end of treatment. Finally, our cohort was comprised of 57 women, aged between 20 and 50 years old, treated with UPA for various conditions (myomas, abnormal bleeding, pelvic pain etc.) during a period of 3 month, and adherence to treatment was 100%. Results for AST are in table 1 and table 2. Results for ALT are in table 3 and table 4. Results for GGT are in table 5 and table 6. Results for TB are in table 7.

Figure 1, 2 and 3 are displaying the distribution of the AST values before and after treatment showing that all values above the upper limit (40UI/L) or (50UI/L) are infrequent and the increase is insignificant (in order to indicate liver impairment they should be doubled). The same results in figure 4 are displaying the distribution of TB values before and after treatment showing that all values above the upper limit of 1.2mg/dL are infrequent.

Safety of UPA administration is a major concern, not only related to the hyperplastic unbalanced estrogen effect on the endometrium, but also to the possible liver function impairment. The UPA metabolism is extensively performed by the liver, 73% of the administered dose is excreted through

![Scheme 1. Structure of Ulipristal acetate[4]](image)

<table>
<thead>
<tr>
<th>Paired Samples Statistics</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST BEFORE</td>
<td>24.07</td>
<td>9.690</td>
<td>1.285</td>
</tr>
<tr>
<td>AST AFTER</td>
<td>24.67</td>
<td>9.551</td>
<td>1.265</td>
</tr>
</tbody>
</table>

Table 1
CORRELATIONS BETWEEN AST BEFORE AND AFTER UPA TREATMENT

<table>
<thead>
<tr>
<th>Paired Samples Test</th>
<th>Paired Differences</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>95% Confidence Interval of the Difference</th>
<th>Lower</th>
<th>Upper</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td>AST BEFORE - AST AFTER</td>
<td>-0.596</td>
<td>13.626</td>
<td>1.805</td>
<td>-4.212</td>
<td>3.019</td>
<td>-3.39</td>
<td>56</td>
<td>.742</td>
</tr>
</tbody>
</table>

Sig. (2-tailed) has a value of 0.742, which is greater than 0.05 (our chosen level of significance), meaning that the initial assumption that there are no significant differences between the 2 sets of data is correct (the null hypothesis is valid).
### Table 3
**Correlations Between ALT Before and After UPA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT Before</td>
<td>24.46</td>
<td>57</td>
<td>10.873</td>
<td>1.440</td>
</tr>
<tr>
<td>ALT After</td>
<td>27.58</td>
<td>57</td>
<td>13.945</td>
<td>1.847</td>
</tr>
</tbody>
</table>

### Table 4
**Paired T-Test for ALT Before and After UPA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Std. Error Mean</td>
</tr>
<tr>
<td>Pair 1</td>
<td>ALT BEFORE</td>
<td>-3.123</td>
<td>17.015</td>
</tr>
<tr>
<td></td>
<td>ALT AFTER</td>
<td>2.254</td>
<td></td>
</tr>
</tbody>
</table>

Sig. (2-tailed) has a value of 0.171, which is greater than 0.05 (our chosen level of significance), meaning that the initial assumption that there are no significant differences between the 2 sets of data is correct (the null hypothesis is valid).

### Table 5
**Correlations Between CGT Before and After UPA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>N</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGT Before</td>
<td>26.54</td>
<td>57</td>
<td>12.211</td>
<td>1.617</td>
</tr>
<tr>
<td>CGT After</td>
<td>26.74</td>
<td>57</td>
<td>12.223</td>
<td>1.619</td>
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</tbody>
</table>

### Table 6
**Paired T-Test for GGT Before and After UPA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Std. Error Mean</td>
</tr>
<tr>
<td>Pair 1</td>
<td>GGT BEFORE</td>
<td>-1.193</td>
<td>16.966</td>
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<td></td>
<td>GGT AFTER</td>
<td>2.247</td>
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</table>

Sig. (2-tailed) has a value of 0.932, which is greater than 0.05 (our chosen level of significance), meaning that the initial assumption that there are no significant differences between the 2 sets of data is correct (the null hypothesis is valid).

### Table 7
**Paired T-Test for TB Before and After UPA Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Paired Differences</th>
<th>95% Confidence Interval of the Difference</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Std. Deviation</td>
<td>Std. Error Mean</td>
</tr>
<tr>
<td>Pair 1</td>
<td>TB BEFORE</td>
<td>-2.2807</td>
<td>1.70102</td>
</tr>
<tr>
<td></td>
<td>TB AFTER</td>
<td>2.2531</td>
<td></td>
</tr>
</tbody>
</table>

Sig. (2-tailed) has a value of 0.316, which is greater than 0.05 (our chosen level of significance), meaning that the initial assumption that there are no significant differences between the 2 sets of data is correct (the null hypothesis is valid). For the total bilirubin values we used nominal values.
potentially harmful effect of UPA on the liver, taking into
mainly after the warning issued by MHRA[19].

toxicity of UPA on the liver function, and the limitation on the study accuracy.

We believe that there is no impact of medical records. Since there was no significant change in potential liver toxic drugs that were not reported in the study.

The limits of our study are given by the small number of enrolled patients. The UPA is recently available in our country, and was well tolerated by those patients [17].

Another study indicated that the UPA exposure is 175,000 patient years, but there were only four cases of severe liver impairment leading to liver transplantation. It is uncertain if there was a previous condition or predisposition, in those cases, to hepatic impairment. During the clinical trials of Esmya, there were no signs of hepatotoxicity, but the protocols provided to exclude the patients with the abnormal values of ALT and AST [18].

In our study, there were no changes in the measured variables after the treatment. We used as indicators for hepatic function the recommended tests that are performed in order to assess hepatic impairment and toxicity and we combined in order to enhance the detection four parameters. EMA recommends a doubling of the normal values, in order to be significant, so, we can assume that there were no hepatic toxic effects of the UPA treatment.

The limits of our study are given by the small number of enrolled patients. The UPA is recently available in our country, and the treatment’s cost is not covered by the National Health Insurance. Given the relative high price of the UPA, it is not affordable for all the patients that could benefit from it.

Another limitation can be the lack of exclusion of other potential liver toxic drugs that were not reported in the medical records. Since there was no significant change in the hepatic function, we believe that there is no impact of the limitation on the study accuracy.

The strong point of the study is the evaluation of the potential toxic effect of UPA on the liver function, and mainly after the warning issued by MHRA[19].

Still, more studies are needed in order to rule out the potential harmful effect of UPA on the liver, taking into

account detailed liver function evaluation, and extended laboratory tests.

Conclusions

In our study the paired T-test determined that there were no statistical significant differences between the liver function after Esmya administration. Although there was no evidence of hepatic impairment in the 3 months course of treatment precautions as recommended by EMA should be respected. The measures include: no use of UPA for women with known liver conditions, careful monitoring of liver function monthly for the patients under treatment and at four weeks after, and immediate discontinuation and report of any adverse complaints.

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19.***Letter from MHRA 09/02/2018 Women taking Esmya for uterine fibroids to have regular liver tests while EMA review is ongoing

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