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Clinical Research Article

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Use of Ulipristal Acetate and Risk of Liver Disease: A Nationwide Cohort Study

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Abbreviations: AE, adverse event; CCI, Charlson Comorbidity Index; EMA, European Medicines Agency; GnRH, gonadotropin-releasing hormone; HIRA, Health Insurance Review and Assessment Service; HR, hazard ratio; PRAC, Pharmacovigilance Risk Assessment Committee; RCT, randomized clinical trial; RR, relative risk; SES, socioeconomic status; UPA, ulipristal acetate.

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Abstract

Context: Large-scale clinical trials on the hepatotoxicity of ulipristal acetate (UPA) are lacking.

Objective: This work aimed to determine the incidence of liver disease with UPA vs gonadotropin-releasing hormone (GnRH) agonists.

Methods: A retrospective cohort study was conducted in South Korea of women with uterine fibroids from the Korean Health Insurance Data 2010 to 2018. Women with uterine fibroids were divided into 2 treatment groups: the UPA (5 mg/day) and GnRH agonist groups. Main outcome measures included the presence or absence of severe liver disease, mild liver disease, and liver transplantation.

Results: Among the patients with uterine fibroids,17 207 patients were treated with GnRH agonists and 20 926 patients with UPA. After 1:1 propensity score matching for each group, there were 11 445 individuals. Neither group had a liver transplantation case. In the conditional logistic regression analysis, the incidence of total liver diseases (relative risk [RR] 1.111; 95% CI, 1.015-1.216) and mild liver diseases (RR 1.094; 95% CI, 1-1.196) was higher in the UPA group than in the GnRH agonist group, but that of severe liver diseases (RR 0.07; 95% CI, 0.001-4.412) and toxic liver disease (RR 1.256; 95% CI, 0.845-1.867) did not differ between the groups.

Conclusion: The incidence of severe liver disease, hepatic failure, and toxic liver disease was not different between the UPA and GnRH agonist groups. However, the incidence of mild liver disease was higher in the UPA group than in the GnRH agonist group. The incidence of hepatic damage with UPA was very low.

Key Words: ulipristal acetate, gonadotropin-releasing hormone agonist, liver, uterine fibroid, cohort

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Uterine fibroids (or leiomyomas) are monoclonal benign tumors of smooth muscle cells in the wall of the uterus and are very common in the field of obstetrics and gynecology, being found in approximately 30% to 70% of reproductive-aged women (1-3). Uterine fibroids cause menorrhagia, dysmenorrhea, pelvic pain, bulk symptoms, a decreased quality of life, and infertility (4).

Traditionally, hysterectomy with definitive cure and myomectomy with fertility preservation have been the main treatments for myoma (3, 5). Recently, high-intensity focused ultrasound and uterine artery embolization have been attempted as less invasive methods for fertility preservation (3, 5).

However, because of the risks associated with surgery and the potential impact on fertility, drug therapy is still an ideal treatment option for uterine fibroids in some women (6). The drugs for uterine fibroids include gonadotropin-releasing hormone (GnRH) agonist, the levonorgestrel-releasing intrauterine system, nonsteroidal anti-inflammatory drugs, oral contraceptives, selective progesterone receptor modulators, and tranexamic acid (2, 3, 5, 7). However, these drugs have been limited to adjuvant treatment because of their various side effects (eg, menopausal symptoms) or therapeutic limitations (2, 3, 5, 7).

Ulipristal acetate (UPA) is an selective progesterone receptor modulator whose effects on reducing the sizes of uterine fibroids and reducing uterine bleeding are excellent (8). Regarding these effects, UPA is not inferior to leuprolide acetate, a GnRH agonist (7). In addition, patients treated with UPA have almost none of the menopausal symptoms (eg, hot flashes, unstable bone turnover marker levels) caused by GnRH agonists (7).

Owing to these therapeutic effects, UPA has been on the market worldwide since 2012, starting in Europe. However, in 2018, in a postmarketing report, the European Medicines Agency (EMA) reported that UPA was prescribed to more than 900 000 people, among whom 8 had serious liver damage and 5 had liver transplantation (6, 9, 10). Because of this risk, the EMA recommended regular liver function tests when using UPA and later discontinued UPA (6, 9, 10). However, large-scale clinical trials of this issue are lacking.

Therefore, the purpose of this study was to compare the incidence of liver disease with UPA and GnRH agonist treatments using Korea's national health claim data.

Materials and Methods

Data

This study is a retrospective nationwide cohort study using Health Insurance Review and Assessment Service (HIRA) data from 2010 to 2018. Korea provides almost all residents national health insurance services for most diseases except cosmetic procedures (11). The HIRA is an institution that determines whether the payment of insurance claims requested by health care service providers is justified and has most of the Korean national health insurance data. The HIRA data include patient age, patient sex, diagnosis, surgery, prescription drugs, hospital information, and health insurance class, among other characteristics.

Selection of Participants

This study used the HIRA Drug Ingredients codes, the International Classification of Diseases, Tenth Revision, and Health Insurance Medical Care Expenses (2017, 2018 version) to screen for specific patients and to specify outcomes.

From October 1, 2013 (the first release date of UPA in Korea), to December 31, 2018, patients with more than 2 diagnostic codes (D25.x) for uterine fibroids and who were prescribed UPA at 5 mg/day were defined as the UPA group. The patients with more than 2 diagnostic codes (D25.x) for uterine fibroids and who were administered GnRH agonist (leuprolide acetate, triptorelin acetate, or goserelin acetate as an approved treatment for uterine fibroids) monthly were defined as the GnRH agonist group.

In each group, patients who underwent myomectomy from 2010 to 2018 or who used one of the drugs in the opposite group (UPA ↔ GnRH agonist) at least once were excluded. Patients with a cancer diagnosis code (C.xx) or liver disease diagnosis code (C22/D015/D134/D376/K70/K71/K72/K73/K74/K75/K76/K778/I85/I864/I982) before the first use of the indicated drugs were excluded in each group. Data from 2010 to 2012 were used to exclude those who had liver disease or had myomectomy during this period.

In addition, patients who were younger than 20 years or older than 50 years in the first year of use of each drug were excluded.

Outcomes

After the first use of the drug, if the same liver disease diagnosis code from the aforementioned list was present 3 or more times (eg, K71, K71, K71), the patient was considered to have each liver disease in the category. If there were 3 or more liver disease diagnosis codes (eg, K71, K72, K73), the patient was considered to have total liver disease. According to the classification method for the Charlson Comorbidity Index (CCI) of Quan et al, mild or severe liver disease was defined as having more than 3 liver diseases in the corresponding category (Table 1) (12). If there was a surgical code (Q8040/Q8041/Q8042/Q8043/Q8044/Q8045/Q8046/Q8047/

Table 1. Diagnostic code according to liver disease category

Category	Diagnostic code, ICD-10
Mild liver disease	B18, K700, K701, K702, K703, K709, K713, K714, K715, K717, K73, K74, K760, K762, K763, K764, K768, K769, Z944
Severe liver disease	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767

ICD, International Classification of Diseases, Tenth Revision.

Q8048/Q8049/Q8050) for liver transplantation, the patient was defined as having a liver transplantation. The period of liver disease incidence was defined from the first prescription (UPA or GnRH agonist) date to the day of the first liver disease diagnosis code or liver transplant surgery code.

Variables

Those eligible for national medical care, such as Medicaid in the United States, were defined as low socioeconomic status (SES). Age was categorized into intervals of 5 years. The period of drug use was categorized into intervals of 3 months or less, 6 months or less, 9 months or less, and 10 months or more. The CCI was calculated from the diagnostic codes from 1 year before the first prescription date (UPA or GnRH agonist) to the first prescription date according to the method of Quan et al and was classified as 0 points, 1 point, or 2 points or more (12). The hospital level was divided into clinic, hospital, and tertiary referral hospital. The UPA use period was the sum of the periods prescribed for UPA, excluding the rest period. For the GnRH agonist, a single injection of 1 month was calculated as 30 days. Uterine fibroids were divided into 4 categories (submucosal, intramural, subserosal, or unspecified) according to the diagnosis code.

Statistics

All statistical analyses in this study were carried out with SAS Enterprise Guide 6.1 (SAS Institute Inc) and R 3.0.1 (The R Foundation for Statistical Computing).

Differences were considered statistically significant if the *P* value was less than .05, and the analyses were 2-sided.

In the data analysis before matching, the chi-square test and Fisher exact test were used for categorical variables, and the *t* test and Mann-Whitney *U* test were used for continuous variables. In the data analysis after matching, the Cochran-Mantel-Haenszel test was used for categorical variables, and the paired *t* test and Wilcoxon signed rank test were used for continuous variables.

For the UPA group and the GnRH agonist group, 1:1 propensity score matching was performed for the first prescribed calendar year, age category (5-year interval), SES, type of uterine myoma, duration of drug use in each group, CCI, and type of medical institution. Conditional logistic regression analysis was performed to compare the effects of the 2 groups on liver disease.

The listwise deletion method was used when the missing value was less than 10%, and the regression imputation method was used when it was 10% or more.

To evaluate the robustness of our findings, stratified Cox regression analysis was performed from the first day of drug use to the first onset day of liver disease.

Ethics

This study was approved by the institutional review board of Eulji Medical Center (EMCS-2019-03-012). This study could not harm any individuals included because variables that could identify individuals were removed. Therefore, there was no need to provide informed consent under the Bioethics and Safety Act of South Korea. Data from this study were provided by the HIRA, but the HIRA has no interest in the results of this study.

Results

From October 1, 2013, to December 31, 2018, there were 17 207 patients treated with GnRH agonist and 20 926 patients treated with UPA among the patients with uterine fibroids. In addition, there were 11 445 individuals after 1:1 propensity score matching for each group (Fig. 1). Before matching, the number of UPA patients was generally higher than that of GnRH agonists every year, but in 2018, the number of UPA patients rapidly decreased (Table 2) (Fig. 2). The average age of the GnRH agonist group before matching was 41.59 ± 0.04 years, and the average age of the UPA group was 43.7 ± 0.04 years ($P < .001$). After matching, all covariates were well balanced below the standardized differences of 0.1 (the propensity-weighted cohort). The detailed characteristics of all patients before and after matching are shown in Table 2.

There was no difference in the incidence of severe liver diseases between both groups regardless of the period (< 6 months: $P = 1$, total period; $P = .865$) (Table 3). There were no liver transplantation cases in either group (see Table 3). Although the incidence of hepatic failure was not significantly different between the 2 groups (total period $P = .479$), 3 cases (0.01%) were found in the only UPA group within 6 months of first drug use. Within 6 months after the first drug use, the UPA group had fewer cases of

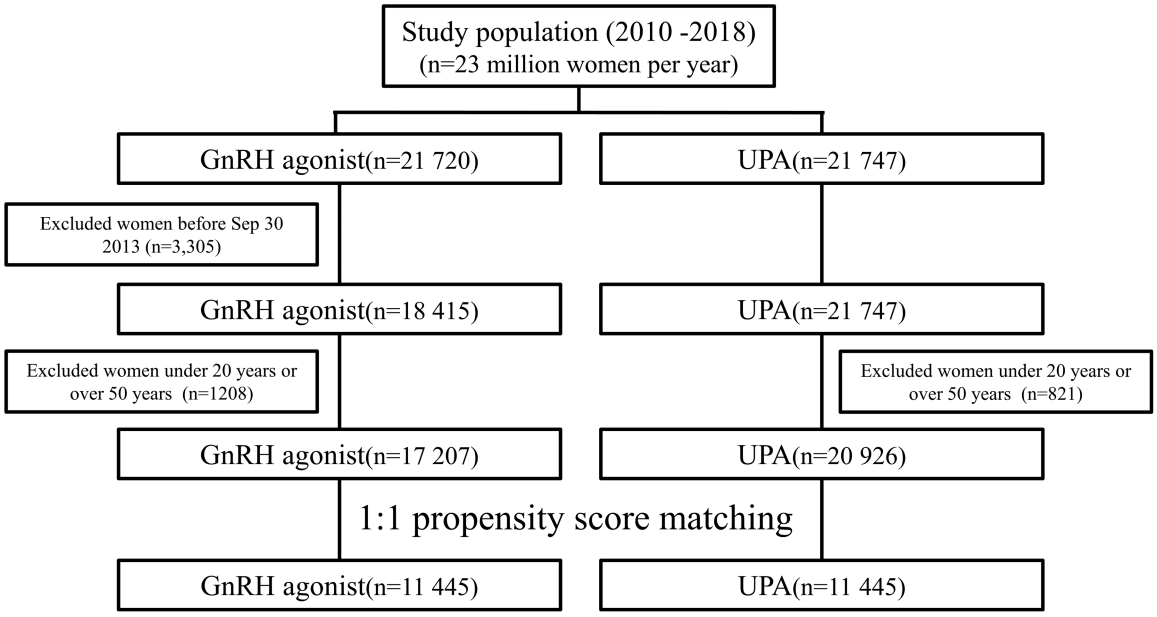

Figure 1. Flowchart to select case-control group according to use of ulipristal acetate (UPA) and gonadotropin-releasing hormone (GnRH) agonist in Health Insurance Review and Assessment Service 2010 to 2018 data.

other inflammatory liver diseases ($P = .011$), mild liver disease ($P = .022$), and total liver diseases ($P = .036$) than the GnRH agonist group. In all periods, the UPA group had more cases of toxic liver disease ($P = .047$), mild liver disease ($P < .001$), other inflammatory liver diseases ($P < .001$), other diseases of the liver ($P < .001$), and total liver diseases ($P < .001$) than the GnRH agonist group. Table 3 shows each liver disease that occurred in each group before matching.

In the conditional logistic regression analysis corrected for 5-year age interval, SES, calendar year of first prescription, duration of drug use, CCI, fibroid type, and medical institution type, the incidence of total liver diseases (relative risk [RR] 1.111; 95% CI, 1.015-1.216) and mild liver diseases (RR 1.094; 95% CI, 1-1.196) was higher in the UPA group than in the GnRH agonist group, but that of severe liver diseases (RR 0.07; 95% CI, 0.001-4.412) and toxic liver disease (RR 1.256; 95% CI, 0.845-1.867) was not different between the groups. In the conditional logistic regression analysis, which focused only on the occurrence of liver disease within 6 months after the first drug administration, there were no differences in the incidence of each liver disease except chronic hepatitis between the 2 groups (Table 4).

There was no difference in the total liver disease incidence between the 2 groups in the survival analysis after matching (Fig. 3) (log-rank test: $P = .116$). The incidence of total liver diseases (hazard ratio [HR] 1.056; 95% CI, 0.965-1.155), mild liver diseases (HR 1.058; 95% CI, 0.96-1.166), and severe liver diseases (HR 0.114; 95% CI, 0.003-4.54) were not different between the 2 groups in the stratified Cox regression analysis with multiple-variable correction (Table 5).

Discussion

There was no difference in the incidence of severe liver disease, hepatic failure, or toxic liver disease between the two groups in this study. No liver transplantations were performed in either group.

Based on our study, more than 4000 patients per year have been treated with UPA in Korea since 2014, which is twice the number of patients treated with GnRH agonist. UPA promotes rapid relief from uterine myoma-related heavy bleeding without estrogen suppression (7).

However, the risks of fatal UPA-induced liver injury leading to liver transplantation have been suggested, and the Pharmacovigilance Risk Assessment Committee (PRAC) has made recommendations restricting its use in new patients or for new treatment courses (10). Nevertheless, the possible mechanism and the class effect of hepatotoxicity have not been elucidated (6). There is an unmet need for alternative medical agents in patients who are not candidates for surgical treatment either because of comorbidities or the risk of infertility (7). This is the first study to investigate the hepatotoxic risk of UPA by assessing nationwide HIRA data from 2013 to 2018 in Korea. The PRAC recommendation was based only on case reports and expert opinion (10). We need more objective, evidence-based opinions considering the large prevalence of uterine myoma

Table 2. Characteristics of women receiving gonadotropin-releasing hormone agonist or gonadotropin-releasing hormone, 2013 to 2018

	UPA vs GnRH agonist								
	No matching				1:1 matching				
	GnRH agonist	UPA	Total	*P*	GnRH agonist	UPA	Total	*P*	Standardized difference
	No. (%)/mean ± SE				No. (%)/mean ± SE				
No. of women	17 207 (45.12)	20 926 (54.88)	38 133 (100)		11 445 (50)	11 445 (50)	22 890 (100)		
Mean age, y	41.59 ± 0.04	43.7 ± 0.04	42.75 ± 0.03	< .001[a]	42.58 ± 0.05	42.70 ± 0.05	42.64 ± 0.04	.088[c]	0.021
Year of first prescription				< .001				1[d]	0
2013[b]	689 (4)	680 (3.25)	1369 (3.59)		364 (3.18)	364 (3.18)	728 (3.18)		
2014	2968 (17.25)	5839 (27.9)	8807 (23.1)		2309 (20.17)	2309 (20.17)	4618 (20.17)		
2015	2896 (16.83)	4131 (19.74)	7207 (18.43)		2187 (19.11)	2187 (19.11)	4374 (19.11)		
2016	3180 (18.48)	4256 (20.34)	7436 (19.5)		2308 (20.17)	2308 (20.17)	4616 (20.17)		
2017	3560 (20.69)	4099 (19.59)	7659 (20.08)		2549 (22.27)	2549 (22.27)	5098 (22.27)		
2018	3914 (22.75)	1921 (9.18)	5835 (15.3)		1728 (15.1)	1728 (15.1)	3456 (15.1)		
Age, 5-y interval				< .001				1[d]	0
21-25	2432 (14.13)	1553 (7.42)	3985 (10.45)		1099 (9.6)	1099 (9.6)	2198 (9.6)		
26-30	3688 (21.43)	2919 (13.95)	6607 (17.33)		2067 (18.06)	2067 (18.06)	4134 (18.06)		
31-35	5251 (30.52)	6185 (29.56)	11 436 (29.99)		3601 (31.46)	3601 (31.46)	7202 (31.46)		
36-40	4527 (26.31)	7474 (35.72)	12 001 (31.47)		3649 (31.88)	3649 (31.88)	7298 (31.88)		
41-45	1239 (7.2)	2642 (12.63)	3881 (10.18)		994 (8.69)	994 (8.69)	1988 (8.69)		
46-50	70 (0.41)	153 (0.73)	223 (0.58)		35 (0.31)	35 (0.31)	70 (0.31)		
SES				.005				.039[d]	0.027
Mid ~ high SES	17039 (99.02)	20658 (98.72)	37697 (98.86)		11332 (99.01)	11299 (98.72)	22631 (98.87)		
Low SES	168 (0.98)	268 (1.28)	436 (1.14)		113 (0.99)	146 (1.28)	259 (1.13)		
Fibroid type				< .001				1[d]	0
Submucosal	1000 (5.81)	1942 (9.28)	2942 (7.72)		709 (6.19)	709 (6.19)	1418 (6.19)		
Intramural	2507 (14.57)	4374 (20.9)	6881 (18.04)		1758 (15.36)	1758 (15.36)	3516 (15.36)		
Subserosal	215 (1.25)	204 (0.97)	419 (1.1)		56 (0.49)	56 (0.49)	112 (0.49)		
Unspecified	13 485 (78.37)	14 406 (68.84)	27 891 (73.14)		8922 (77.96)	8922 (77.96)	17 844 (77.96)		
Duration of drug use, mo				< .001				1[d]	0
≤ 3	14 294 (83.07)	15 806 (75.53)	30 100 (78.93)		9545 (83.4)	9545 (83.4)	19 090 (83.4)		
≤ 6	2718 (15.8)	3500 (16.73)	6218 (16.31)		1752 (15.31)	1752 (15.31)	3504 (15.31)		
≤ 9	146 (0.85)	942 (4.5)	1088 (2.85)		111 (0.97)	111 (0.97)	222 (0.97)		
10 ~	49 (0.28)	678 (3.24)	727 (1.91)		37 (0.32)	37 (0.32)	74 (0.32)		
CCI				< .001				1[d]	0
0	14 560 (84.62)	17 651 (84.35)	32 211 (84.47)		9859 (86.41)	9859 (86.41)	19 718 (86.41)		
1	2191 (12.73)	2910 (13.91)	5101 (13.38)		1452 (12.69)	1452 (12.69)	2904 (12.69)		
2 ~	456 (2.65)	365 (1.74)	821 (2.15)		134 (1.17)	134 (1.17)	268 (1.17)		

Table 2. Continued

	UPA vs GnRH agonist						
	No matching				1:1 matching		
	GnRH agonist	UPA	Total	*P*	GnRH agonist	UPA	Total	*P*	Standardized difference
	No. (%)/mean ± SE				No. (%)/mean ± SE				
Medical institution				< .001				1[d]	0
Clinic	5768 (33.52)	12 126 (57.95)	17 894 (46.93)		5214 (45.56)	5214 (45.56)	10 428 (45.56)		
Hospital	5067 (29.45)	3296 (15.75)	8363 (21.93)		2387 (20.86)	2387 (20.86)	4774 (20.86)		
Tertiary referral hospital	6372 (37.03)	5504 (26.3)	11 876 (31.14)		3844 (33.59)	3844 (33.59)	7688 (33.59)		

Abbreviations: CCI, Charlson Comorbidity Index; GnRH agonist, gonadotropin-releasing hormone agonist; SES, socioeconomic status; UPA, ulipristal acetate.
[a]Obtained with Mann-Whitney *U* test.
[b]Period from October 1, 2019 (first UPA prescription date) to December 31, 2019.
[c]Obtained with Wilcoxon signed rank test.
[d]Obtained with Cochran-Mantel-Haenszel test.

Figure 2. The trend in prescription according to year increments in Health Insurance Review and Assessment Service 2013 to 2018 data. GnRH, gonadotropin-releasing hormone; UPA, ulipristal acetate.

patients who necessitate treatment and the very rare incidence of fatal hepatotoxicity.

The results of this study showed that 0.04% of severe liver disease and hepatic failure occurred in the UPA group, and no liver transplantations were performed. Among 1053 patients who used UPA in the PEARL I to IV studies, there were 4 cases of liver disorder-related adverse events (AEs) but no cases of hepatotoxicity (6, 7, 13-16). There were no severe AEs associated with the liver among 519 patients who used UPA in 4 randomized clinical trials (RCTs) other than the PEARL trials (17-20). As such, there was no severe AE-related hepatotoxicity in the RCTs (7, 13-20). This difference seems to be because the RCTs excluded patients with abnormalities by means of stricter liver function blood tests. Additionally, a relatively small number of patients would have been affected, unlike the EMA report or this study. EMA data showed that 8 out of 765 000 patients (1 per 100 000) had severe liver damage, and 5 out of more than 900 000 patients (less than 0.6 per 100 000) reported liver transplantation (10). Direct comparisons are difficult because the definitions of severe liver diseases in this study and previous studies are inconsistent. However, the results of this study also confirmed that severe liver diseases that require liver transplantation, such as those in the EMA data, are very rare. Considering that the mortality rate from penicillin allergies is 2 per 100 000, it is necessary to discuss whether UPA should be allowed clinically (10).

In this study, there was no difference in the incidence of severe liver disease (RR 0.07; 95% CI, 0.001-4.412), hepatic failure (RR 0; 95% CI, 0-infinite), or toxic liver disease (RR 1.256; 95% CI, 0.845-1.867) between the 2 groups in this study (see Tables 3 and 4). Previous studies comparing UPA and GnRH agonist groups did not perform statistical comparative analyses because the comparison of liver disorder–related severe AEs was not the main outcome (7, 19, 20). The reason there is no difference in the incidence of severe liver disease between the 2 groups is presumed as follows. First, this may be because the number of patients

Table 3. Liver disease according to treatment method in the Health Insurance Review and Assessment Service 2013 to 2018 data set (before matching)

Liver diseases	GnRH agonist (n = 17 207)							UPA (n = 20 867)							Total	*P*[a]	
	Mo					Subtotal		Mo					Subtotal				
	~ 3	4 ~ 6	7 ~ 9	10 ~ 12	> 12	< 6 mo	Total period	~ 3	4 ~ 6	7 ~ 9	10 ~ 12	> 12	< 6 mo	Total period		< 6 mo	Total period
Alcoholic liver disease	4	3	3	5	21	7 (0.04)	36 (0.21)	8	4	6	2	39	12 (0.06)	59 (0.28)	95 (0.25)	.464	.156
Toxic liver disease	25	9	3	6	40	34 (0.2)	83 (0.48)	17	17	3	8	88	34 (0.16)	133 (0.64)	216 (0.57)	.425	.047
Hepatic failure	0	0	0	1	4	0 (0)	5 (0.03)	1	2	0	0	6	3 (0.01)	9 (0.04)	14 (0.04)	.257	.479
Chronic hepatitis	40	16	12	10	90	56 (0.33)	168 (0.98)	27	16	12	14	140	43 (0.21)	209 (1)	377 (0.99)	.023	.826
Fibrosis and cirrhosis of liver	2	0	3	1	10	2 (0.01)	16 (0.09)	1	3	2	1	8	4 (0.02)	15 (0.07)	31 (0.08)	.696	.468
Other inflammatory liver diseases	59	24	13	19	147	83 (0.48)	262 (1.52)	50	33	34	22	288	83 (0.4)	427 (2.04)	689 (1.81)	.212	< .001
Other diseases of liver	284	130	96	87	687	414 (2.41)	1284 (7.46)	251	171	166	182	1285	422 (2.02)	2055 (9.82)	3339 (8.76)	.011	< .001
Liver disorders in other diseases classified elsewhere	3	1	1	0	8	4 (0.02)	13 (0.08)	3	3	1	2	9	6 (0.03)	18 (0.09)	31 (0.08)	1	.721
Esophageal and gastric varices	0	0	0	0	1	0 (0)	1 (0.01)	0	0	0	0	0	0 (0)	0 (0)	1 (0)	1	.451[b]
Esophageal varices without bleeding in diseases classified elsewhere	0	0	0	0	0	0 (0)	0 (0)	0	0	0	0	0	0 (0)	0 (0)	0 (0)	1	1
Gastric varices	0	0	0	0	0	0 (0)	0 (0)	0	0	0	0	0	0 (0)	0 (0)	0 (0)	1	1
Mild liver diseases	313	143	105	99	759	456 (2.65)	1419 (8.25)	282	195	179	194	1392	477 (2.29)	2242 (10.71)	3661 (9.6)	0.022	< .001
Severe liver diseases	0	0	0	1	5	0 (0)	6 (0.03)	0	1	0	0	7	1 (0)	8 (0.04)	14 (0.04)	1	.865
Carcinoma in situ of liver, GB and BD	0	0	0	0	0	0 (0)	0 (0)	0	1	0	0	0	1 (0)	1 (0)	1 (0)	1	1[b]
Benign neoplasm of intrahepatic BD	4	3	4	1	31	7 (0.04)	43 (0.25)	9	8	4	6	43	17 (0.08)	70 (0.33)	113 (0.3)	.115	.13
Neoplasm of unknown behavior of liver, GB and BD	2	2	1	0	8	4 (0.02)	13 (0.08)	0	1	0	3	14	1 (0)	18 (0.09)	31 (0.08)	.183	.721
Malignant neoplasm of liver and intrahepatic BD	2	1	1	0	5	3 (0.02)	9 (0.05)	0	2	0	1	9	2 (0.01)	12 (0.06)	21 (0.06)	.664	.835
Liver transplantation	0	0	0	0	0	0 (0)	0 (0)	0	0	0	0	0	0 (0)	0 (0)	0 (0)	1	1
Total liver disease	377	165	120	119	893	542 (3.15)	1674 (9.73)	342	239	210	224	1638	581 (2.78)	2653 (12.68)	4327 (11.35)	.036	< .001

Data are expressed as the number (%).

Abbreviations: BD, bile ducts; GB, gallbladder; GnRH agonist, gonadotropin-releasing hormone agonist; UPA, ulipristal acetate.

[a]This is a 2 × 2 categorical analysis according to one liver disease and drug class.

[b]Obtained with Fisher exact test.

Table 4. Relative risk of uterine fibroids according to treatment method from the Health Insurance Review and Assessment Service 2013 to 2018 data set (after matching)

	UPA vs GnRH agonist							
	Within 6 mo after first drug use				Total period after first drug use			
	RR	Lower CI	Upper CI	*P*	RR	Lower CI	Upper CI	*P*
Alcoholic liver disease[a]	3.874	0.463	32.056	.211	1.164	0.642	2.105	.618
Toxic liver disease[a]	0.759	0.387	1.487	.422	1.256	0.845	1.867	.26
Hepatic failure[a]	0	0	Infinite	1	0	0	Infinite	.996
Chronic hepatitis[a]	0.510	0.273	0.950	.034	0.875	0.656	1.167	.366
Fibrosis and cirrhosis of liver[a]	Infinite	0	Infinite	1	1.032	0.358	2.969	.953
Other inflammatory liver diseases[a]	0.859	0.540	1.364	.52	1.161	0.926	1.453	.195
Other diseases of liver[a]	0.902	0.749	1.087	.278	1.106	1.007	1.214	.035
Liver disorders in other diseases classified elsewhere[a]	0.821	0.062	10.878	.881	0.727	0.286	1.848	.503
Esophageal and gastric varices[a]					0	0	Infinite	1
Mild liver diseases[a]	0.913	0.764	1.090	.315	1.094	1.000	1.196	.049
Severe liver diseases[a]					0.070	0.001	4.412	.208
Carcinoma in situ of liver, GB, and BD[a]	Infinite	0	Infinite	1	Infinite	0	Infinite	1
Benign neoplasm of intrahepatic BD[a]	22.697	0.375	Infinite	.136	1.426	0.818	2.485	.21
Neoplasm of unknown behavior of liver, GB, and BD[a]	0.000	0.000	Infinite	1	2.242	0.492	10.158	.296
Malignant neoplasm of liver and intrahepatic BD[a]	0.000	0.000	Infinite	1	1.255	0.385	4.080	.707
Total liver disease[a]	0.947	0.803	1.117	.521	1.111	1.015	1.216	.023

Some liver diseases not shown in this table were not analyzed because of the small number of cases.

Abbreviations: BD, bile ducts; CCI, Charlson Comorbidity Index; GB, gallbladder; GnRH agonist, gonadotropin-releasing hormone agonist; RR, relative risk; SES, socioeconomic status; UPA, ulipristal acetate.

[a]Formula: liver disease ~ drug + patients age per 5-y interval + SES + calendar y of first drug use + duration of drug use (mo) + CCI + fibroids + medical institution type.

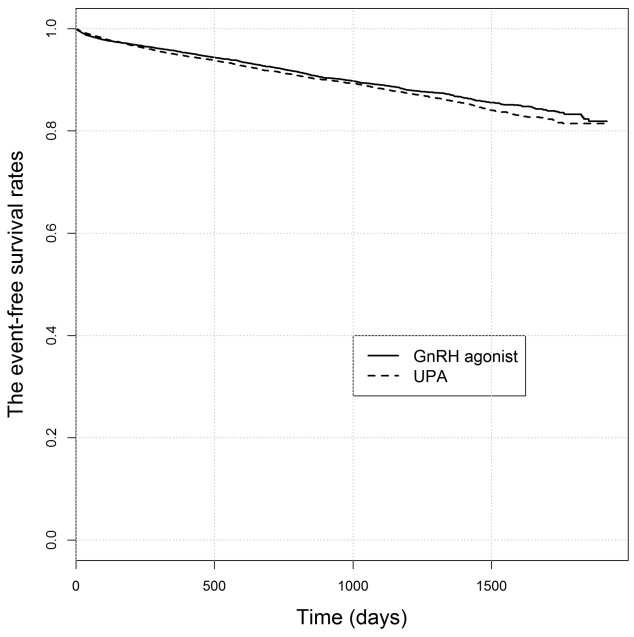

Figure 3. The survival curves of patient with total liver diseases after first drug use according to drug type from the Health Insurance Review and Assessment Service 2013 to 2018 data set (after matching).

in this study is smaller than the number of individuals in the EMA report. In the EMA data, liver transplantation occurred in 6 patients per 1 000 000. Therefore, one liver transplantation occurs in at least 100 000 to 200 000 UPA patients. However, the UPA group included only 20 926 patients in this study. Second, there may be racial differences in the drug response. Third, UPA may not have serious liver toxicity. It seems that more large-scale research is needed.

There were 3675 patients who developed mild and severe liver diseases within the first 6 months of medical treatment for uterine myoma. However, mild or severe liver diseases based on the CCI require more than 6 months to develop. Therefore, it would be unlikely to be related to either UPA or GnRH agonist use in this short period of time.

The incidence of toxic liver disease was significantly higher in the UPA-treated group during the total treatment period but not during the first 6 months of treatment. We postulate that UPA-related hepatotoxicity does not appear in the form of a dose-dependent, intrinsic reaction, as suggested by Donnez et al (6). It is well known that apart from the intrinsic toxic effects of the drug itself, other factors can make the host vulnerable to idiosyncratic hepatotoxicity (21). The reported incidence of UPA toxicity is approximately 0.01% (8 out of more than 76 500 patients) (6). However, it would be essential to evaluate the parameters of UPA-affected patients, including genetic factors, to draw an objective conclusion of the hepatotoxic risk of UPA treatment.

Table 5. Stratified Cox regression analysis for uterine fibroids according to treatment method from the Health Insurance Review and Assessment Service 2013 to 2018 data set (after matching)

	HR	Lower CI	Upper CI	*P*
Mild liver diseases	1.058	0.96	1.166	.252
Severe liver diseases	0.114	0.003	4.54	.248
Malignant neoplasm of liver and intrahepatic BD	1.097	0.319	3.77	.883
Total liver disease	1.056	0.965	1.155	.235

Abbreviations: BD, bile ducts; HR, hazard ratio.

The incidence of "other inflammatory liver disease (K75)" was higher in the UPA-treated group when the total treatment period was assessed. Among the liver diseases coded as K75, we assume that liver abscess would be the majority, based on the high prevalence of liver abscess (K75.0) (64.3% in total "other inflammatory liver disease [K75]": 106 754 [K75.0]/166 118 [K75] patients hospitalized in 2018) (22). Therefore, the effect would be far from the hepatotoxicity of UPA.

The development of "other diseases of the liver (K76)" and total liver disease were significantly higher in the UPA-treated patients both in the first 6 months and total period of treatment. Additionally, odds ratios of "other disease of the liver" and total liver disease were significant for UPA treatment when conditional logistic regression analysis was performed after matching the baseline data between the 2 treatments. An atypical form of toxic liver disease could have been coded as this liver disease category. We cannot deny the possible relationship between UPA and the development of this atypical liver disease.

Strengths and Limitations

Although the EMA report is based on many patients, it is a postmarketing report without a control group; therefore, a strength of our study is that it includes a control group of patients treated with a GnRH agonist. Additionally, the study is based on nationwide claim data that are more representative of real-life practice. Differently from the EMA data, we found that incidences of severe liver injuries were not different between the 2 groups.

There are several limitations in this study. First, we classified the severity of liver disease based on the CCI. However, we were not able to assess the magnitude of hepatotoxicity of UPA by this classification because these codes were not designed to assess acute liver injury. Apart from their meaning, liver cirrhosis is the prerequisite for the CCI classification. Additionally, severity was assessed by the presence of portal hypertension and/or variceal hemorrhage (23, 24). Further real-life data based on a large cohort of patients or systematic reviews are needed to draw conclusions regarding the severity of UPA hepatotoxicity. Second, we could not postulate the possible mechanism or class effect of UPA-related hepatotoxicity in our study because of the nature of the big data. Third, there could be missing data due to inappropriate disease coding, which is very common in real-life practice. Minimally, the incidence of hepatic failure was not different between the 2 treatment groups. Additionally, there was no case of liver transplantation from 2010 to 2018 among patients who were treated with UPA, suggesting the very low incidence of fatal liver toxicity in real-life practice. Finally, the overall durations of treatments were relatively short (75%-83% of the cohort were treated within 3 months). This may prevent recognition of severe liver disease associated with long-term use. However, the short-term use analyzed in this study reflects the real-world clinical situation.

Conclusion

The incidence of severe liver disease, hepatic failure, and toxic liver disease was not different between the UPA and GnRH agonist groups. However, the incidence of mild liver disease was higher in the UPA group than in the GnRH agonist group. No liver transplantations were performed in either group. The incidence of hepatic damage with UPA was very low.

Additional Information

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Data Availability: In accordance with HIRA's privacy policy, our raw data are analyzed and stored only within HIRA's private servers. Therefore, only someone with HIRA's permission can access the raw data. Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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