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Incidence and Pattern of Aminotransferase Elevation During Anti-Hypertensive Therapy With Angiotensin-II Receptor Blockers

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ABSTRACT

Background: Angiotensin type II receptor blockers (ARBs) are the most widely used anti-hypertensive drugs. This study aimed to elucidate the likelihood and pattern of ARB-induced liver injury in a hospital-based cohort.
Methods: Data of patients receiving fimasartan (n = 5,543), candesartan (n = 6,406), valsartan (n = 6,040), and losartan (n = 9,126) were retrieved from the clinical data warehouse of two tertiary hospitals. Patients with alanine aminotransferase (ALT) levels > 5 times the upper normal limit were assessed according to the Roussel Uclaf Causality Assessment Method (RUCAM).
Results: A total of 27,115 patients were enrolled, including 14,630 (54.0%) men, with a mean age of 64.6 years (standard deviation, 13.6). During 31,717 person-years of ARB therapy, serum ALT levels > 120 IU/L were found in 558 (2.1%) person-years, and levels > 200 IU/L were found in 155 (0.6%) person-years. The incidence of ALT elevation > 120 IU/L per 10^6 cumulative defined daily doses was 6.6, 3.6, 3.9, and 4.0 in the fimasartan, candesartan, valsartan, and losartan groups, respectively ($P = 0.002$). An ALT level > 200 IU/L with RUCAM score ≥ 6 was found in 20 patients, suggesting probable drug-induced liver injury for 11 (0.2%) patients receiving fimasartan, five (0.1%) receiving candesartan, four (0.1%) receiving valsartan, and none receiving losartan ($P < 0.001$).
Conclusion: Approximately 2% of patients receiving ARB therapy had significant ALT elevation (4.24/10^6 cumulative defined daily doses [cDDDs]), which was associated with probable ARB-related liver injury in 0.07% of patients (0.15/10^6 cDDDs). Elevation of ALT was more commonly associated with fimasartan than the other ARBs. Clinicians should be aware of the possibility of ARB-related ALT elevation in patients with unexplained chronic abnormal ALT.

Keywords: Chemical and Drug Induced Liver Injury; Angiotensin II Type 2 Receptor Blockers; Alanine Transaminase; Liver Function Tests; Fimasartan

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INTRODUCTION

Angiotensin type II receptor blockers (ARBs) are one of the most effective anti-hypertensive drugs. Consequently, since hypertension is a highly prevalent disease and a major factor for cardiovascular morbidity and mortality, ARBs are widely used.[1] In 2020 the global ARB market was valued at 7.87 billion USD and this expected to exceed 10 billion USD in the future.[2] Of the 9.5 million patients receiving anti-hypertensive treatment in Korea annually, ARBs are the most commonly used drug (72.5%), followed by calcium channel blockers (60.9%), diuretics (24.7%), and beta-blockers (15.7%).[3]

Abnormal aminotransferase levels are sometimes found in patients with hypertension. As patients with hypertension may take several medications simultaneously, clinicians may subsequently consider discontinuing some drugs. Most ARBs, such as losartan,[4] valsartan,[5] and candesartan,[6] follow renal elimination pathways, so they have been associated with rates of liver function abnormalities reported to be no higher than the rates of placebo therapy (< 2%). According to previous reports, liver enzyme elevation is usually transient, exhibits as a hepatitis-like syndrome with hepatocellular or cholestatic pattern, and has an onset of 1 to 8 weeks from treatment initiation.[4-6]

Unlike classical ARBs, fimasartan is a recently developed nonpeptide ARB with a highly selective angiotensin II receptor type 1 affinity. Fimasartan shows rapid absorption following oral intake, with a time to peak plasma concentration ranging from 0.5 to 3 hours.[7] Fimasartan is mainly excreted unchanged through bile by multiple cytochrome p450s, mainly CYP3A, and less than 3% is excreted in urine. Fimasartan has excellent efficacy in controlling hypertension,[8] but the pharmacokinetics of the drug have raised concerns regarding the increased possibility of drug-induced liver injury (DILI). To date, few case reports have described ARB-induced liver injury.[9-12] Most cohort studies have not reported detailed liver injury incidence and outcomes related to ARB-related DILI, instead only the overall, severe adverse drug-related reaction rates have been reported.[8]

This study was conducted to assess the likelihood of hepatic impairment and to elucidate the pattern of ARB-induced liver injury in a large hospital-based cohort.

METHODS

Patients and study design

In this multicenter retrospective cohort study, we retrieved patient data from the Clinical Data Warehouse (CDW) of Seoul National University Bundang Hospital and Kyung Hee University Medical Center. Patients taking ARBs, including losartan, valsartan, fimasartan, and candesartan, for more than five days from 1 January 2015 to 31 December 2020 were enrolled in this study. If the patients received multiple ARBs during this period, we only obtained data associated with the first drug administered. **Fig. 1** shows a flowchart of the study population. Of 42,278 patients prescribed ARBs (fimasartan, candesartan, valsartan, and losartan) during this period, 15,163 were excluded from the analysis. The exclusion criteria were: diagnosis of chronic hepatitis B (n = 684), chronic hepatitis C (n = 198), alcoholic liver disease (n = 46), autoimmune hepatitis (n = 79), other viral hepatitis (n = 15), liver cirrhosis (n = 572), hepatobiliary malignancy (n = 561), obstructive hepatobiliary disease (n = 466), and ischemic hepatitis (n = 30). Patients without baseline alanine aminotransferase

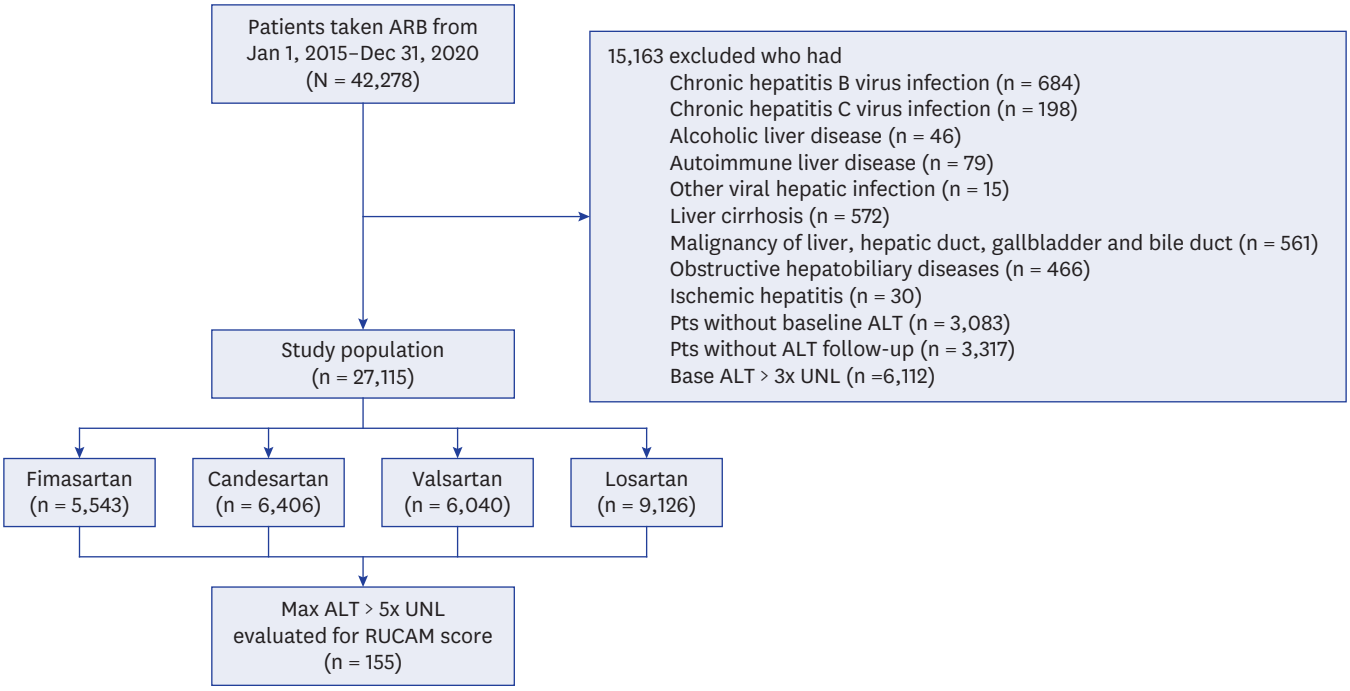

Fig. 1. Flowchart of patient selection.
ARB = angiotensin type II receptor blocker, ALT = alanine aminotransferase, UNL = upper normal limit (40 IU/L), RUCAM = Roussel Uclaf Causality Assessment Method.

(ALT) level data (n = 3,083), those with only one ALT level (n = 3,317), and those with a baseline ALT > 120 IU/L were also excluded (**Fig. 1**).

Patient characteristics were evaluated for age, sex, and comorbidities, such as diabetes mellitus (DM) and fatty liver disease. Diabetes mellitus was defined by International Classification of Diseases, Tenth Revision (ICD-10) codes E08–E13 or with a prescription history of anti-diabetic medication. Fatty liver disease was defined by ICD-10 code K76.0, or the presence of fatty liver disease on imaging such as abdominal sonography, abdominal computed tomography, or magnetic resonance imaging. The co-administration of metformin or statins with ARB was also documented. Baseline laboratory measures were retrieved. Baseline laboratory data were defined when samples were collected within 90 days prior to the ARB initiation. Baseline laboratory data included aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), cholesterol, gamma-glutamyl transferase, glucose, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c (HbA1c), total bilirubin, and triglyceride (TG).

Grading of aminotransferase elevation & assessment of causality

Serum ALT values obtained during ARB therapy were retrieved from the CDW. Using this, we identified the baseline, maximum, and last ALT values, which were the last records before cessation of ARB therapy or the final follow-up. 'Significant' ALT elevation was defined when the maximum ALT was > 120 IU/L, and 'severe' ALT elevation was defined when the maximum ALT was > 200 IU/L, which is a DILI case definition suggested by EASL clinical practice guideline.[13] Patients who had severe ALT elevation while taking ARB were further evaluated using the Roussel Uclaf Causality Assessment Method (RUCAM) scale by an independent hepatologist (WJC, GAK, YP, JJS, or ESJ), who was not involved in direct patient care and was blinded to the final diagnosis of the ALT abnormality.[13,14] Additionally, hard-to-determine cases were discussed with the other experts.

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Statistical analysis

Baseline characteristics and laboratory results are described as mean ± standard deviation (SD) for continuous variables and as frequencies (percentages) for categorical variables. According to the World Health Organization, the cumulative defined daily dose (cDDD) was calculated for each ARB by multiplying the drug duration with a defined daily dose corresponding to the Anatomical Therapeutic Chemical code. The incidence rate of significant or severe ALT elevation and ARB-related liver injury was calculated per 10^6 cDDDs. The incidence rate ratio (IRR) of significant or severe ALT elevation and ARB-related liver injury by ARB group was calculated using Poisson regression analysis. The baseline characteristics of patients were compared between the groups with and without significant ALT elevation (> 120 IU/L) using the t-test for continuous variables and χ^2 test for categorical variables. The Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of significant ALT elevation during ARB therapy. Statistical significance was defined as $P < 0.05$. STATA version 16.0 (StataCorp, College Station, TX, USA) was used to perform all statistical analyses.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-2102-664-007), and the requirement for informed consent was waived due to the retrospective nature of this study.

RESULTS

Baseline characteristics of study population according to ARB groups

A total of 27,115 patients were included, 14,630 (54.0%) were men and the mean age was 64.6 ± 13.6 years. The median duration of ARB therapy was 203 days (interquartile range, 45–623). As shown in **Table 1**, patient age, treatment duration, cDDD, the frequency of comorbidities, and co-medication with statins or metformin differed significantly between the ARB groups. Patients in the fimasartan group were younger (63.5 ± 13.9 years old) and were less likely to also have DM (36.1%) than patients in the other groups and these findings were statistically significant ($P < 0.001$). The percentages of patients taking statins were 69.2%, 72.4%, 73.2%, and 64.6% in the fimasartan, candesartan, valsartan, and losartan groups, respectively ($P < 0.001$). The percentages of patients taking metformin were 26.0%, 30.6%, 30.9%, and 29.3% in the fimasartan, candesartan, valsartan, and losartan groups, respectively ($P < 0.001$). Valsartan was the most prescribed ARB by clinicians in the neurology department (39.2%), and losartan was the most prescribed ARB by clinicians in the nephrology department (46.9%; **Table 1**).

Incidence of ALT elevation during ARB therapy

For 31,717 person-years (PYs) of ARB therapy, significant serum ALT elevation was found in 558 cases (2.1%, 17.6/1,000 PY, 4.24/10^6 cDDDs), and severe ALT elevation was found in 155 cases (0.6%, 4.89/1,000 PY, 1.18/10^6 cDDDs). The incidence of significant ALT elevation was 6.6, 3.6, 3.9 and 4.0 per 10^6 cDDD in the fimasartan, candesartan, and losartan groups, respectively ($P = 0.002$), and the IRR of the fimasartan group compared to the losartan group was 1.64 (95% CI, 1.30–2.07; $P < 0.001$) (**Table 2**). The incidence of severe ALT elevation was not significantly different among ARB groups ($P = 0.489$). However, the IRR of severe ALT elevation in the valsartan group compared to that in the losartan group was 0.44 (95% CI, 0.27–0.70; $P = 0.001$) (**Table 2**).

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Table 1. Baseline characteristics of the study population

Characteristics	Total (N = 27,115)	Fimasartan (n = 5,543)	Candesartan (n = 6,406)	Valsartan (n = 6,040)	Losartan (n = 9,126)	*P* value
Age, yr	64.6 ± 13.6	63.5 ± 13.9	64.7 ± 13.6	64.2 ± 12.4	65.5 ± 14.0	< 0.001***
Male	14,630 (54.0)	3,006 (54.2)	3,427 (53.5)	3,227 (53.4)	4,970 (54.5)	0.508
Duration of medication, days	432.7 ± 516.3	372.9 ± 454.8	461.1 ± 526.2	568.6 ± 545.6	359.1 ± 504.7	< 0.001***
cDDD	492.3 ± 656.8	360.8 ± 512.1	550.1 ± 682.7	600.6 ± 639.7	459.9 ± 709.2	< 0.001***
Underlying co-morbidity						
Diabetes mellitus	11,111 (41.0)	1,998 (36.1)	2,786 (43.5)	2,588 (42.9)	3,739 (41.0)	< 0.001***
Fatty liver disease	1,852/7,683 (24.1)	344/1,434 (24.0)	431/1,670 (25.8)	392/913 (42.9)	685/3,666 (18.7)	< 0.001***
Co-medication						
Statins	18,784 (69.3)	3,834 (69.2)	4,639 (72.4)	4,420 (73.2)	5,891 (64.6)	< 0.001***
Metformin	7,943 (29.3)	1,441 (26.0)	1,960 (30.6)	1,868 (30.9)	2,674 (29.3)	< 0.001***
Primary department of prescription[a]						< 0.001***
Cardiology	10,953 (40.4)	2,663 (24.3)	3,156 (28.8)	2,390 (21.8)	2,744 (25.1)	
Neurology	4,115 (15.2)	958 (23.3)	701 (17.0)	1,614 (39.2)	842 (20.5)	
Nephrology	3,190 (11.8)	555 (17.4)	618 (19.4)	522 (16.4)	1,495 (46.9)	
Endocrinology	2,710 (10.0)	373 (13.7)	807 (29.8)	756 (27.9)	774 (28.6)	
Neurologic surgery	960 (3.5)	231 (24.1)	143 (14.9)	25 (2.6)	561 (58.4)	
General surgery	980 (3.6)	70 (7.1)	132 (13.5)	303 (30.9)	475 (48.5)	
Geriatric center	542 (2.0)	168 (31.0)	101 (18.6)	66 (12.2)	207 (38.2)	
Family medicine	452 (1.7)	48 (10.6)	164 (36.3)	145 (32.1)	95 (21.0)	
Others	3,213 (11.9)	477 (14.9)	584 (18.2)	219 (6.8)	1,933 (60.2)	
Baseline laboratory findings						
AST, IU/L	28.0 ± 16.6	28.0 ± 16.2	27.8 ± 14.7	28.0 ± 15.0	28.1 ± 19.1	0.786
ALT, IU/L	25.1 ± 17.2	25.6 ± 17.2	25.2 ± 17.0	25.4 ± 17.2	24.5 ± 17.2	0.002**
ALP, IU/L (n = 23,972)	80.2 ± 39.8	80.0 ± 39.1	79.2 ± 38.6	79.2 ± 41.4	81.9 ± 39.8	< 0.001***
Total bilirubin, mg/dL (n = 20,012)	0.74 ± 0.48	0.73 ± 0.52	0.74 ± 0.39	0.77 ± 0.34	0.72 ± 0.54	< 0.001***
GGT, IU/L (n = 11,798)	46.3 ± 73.5	42.8 ± 52.4	45.1 ± 73.5	45.4 ± 60.0	50.6 ± 94.2	< 0.001***
Glucose, mg/dL (n = 19,746)	125.6 ± 49.5	123.1 ± 46.7	125.7 ± 50.1	119.9 ± 41.8	128.4 ± 52.2	< 0.001***
HbA1c, % (n = 12,840)	6.5 ± 1.35	6.34 ± 1.29	6.47 ± 1.29	6.52 ± 1.22	6.59 ± 1.45	< 0.001***
Total cholesterol, mg/dL (n = 20,005)	164.4 ± 43.4	170.5 ± 45.1	162.1 ± 42.6	163.8 ± 39.5	162.8 ± 43.9	< 0.001***
TG, mg/dL (n = 17,195)	140.8 ± 99.4	142.0 ± 93.8	139.8 ± 105.2	145.8 ± 106.8	136.7 ± 91.6	< 0.001***
HDL, mg/dL (n = 16,469)	49.1 ± 12.6	50.1 ± 12.6	49.0 ± 12.3	50.2 ± 12.9	47.6 ± 12.4	< 0.001***
LDL, mg/dL (n = 16,384)	97.1 ± 32.2	101.4 ± 32.8	96.0 ± 32.0	97.1 ± 32.6	95.0 ± 31.4	< 0.001***

Values are presented as mean ± standard deviation or number (%).
cDDD = cumulative daily drug dose, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phophatase, GGT = gamma glutamyltransferase, HbA1c = hemoglobin A1c, TG = triglyceride, HDL = high density lipoprotein, LDL = low density lipoprotein.
[a]Percentage is a proportion of patients who mainly prescribed the drug within each department.
*P < 0.05, **P < 0.01, ***P < 0.001.

Table 2. Frequencies of ALT elevation during angiotensin receptor blocker therapy

Variables	Total (N = 27,115)	Fimasartan (n = 5,543)	Candesartan (n = 6,406)	Valsartan (n = 6,040)	Losartan (n = 9,126)	*P* value
cDDDs	13,186,753	1,963,998.5	3,482,864.5	3,597,274.5	4,134,937	
Person-years	31,717.2	5,551.0	7,992.9	9,338.0	8,835.3	
Maxumum ALT > 3x UNL	558 (2.06)	129 (2.33)	125 (1.95)	140 (2.32)	164 (1.80)	0.047*
Incidence, per 10^6 cDDDs (95% CI)	4.24 (3.90–4.60)	6.57 (5.53–7.80)	3.59 (3.01–4.28)	3.90 (3.31–4.60)	3.97 (3.41–4.62)	0.002**
IRR[a] (95% CI)		1.64 (1.30–2.07)	0.90 (0.72–1.14)	1.00 (0.80–1.25)	1.00	
Maximum ALT > 5x UNL	155 (0.57)	37 (0.67)	35 (0.55)	23 (0.38)	60 (0.66)	0.098
Incidence, per 10^6 cDDDs (95% CI)	1.18 (1.00–1.38)	1.88 (1.36–2.60)	1.00 (0.72–1.40)	0.64 (0.42–0.96)	1.45 (1.13–1.87)	0.489
IRR[a] (95% CI)		1.27 (0.85–1.92)	0.68 (0.45–1.04)	0.44 (0.27–0.70)	1.00	
RUCAM scale above 6	20 (0.07)	11 (0.2)	5 (0.08)	4 (0.07)	0 (0.0)	< 0.001***
Incidence, per 10^6 cDDDs (95% CI)	0.15 (0.10–0.24)	0.56 (0.31–1.01)	0.14 (0.06–0.34)	0.11 (0.04–0.29)	-	
RUCAM scale above 9	7 (0.03)	6 (0.11)	1 (0.01)	0 (0.0)	0 (0.0)	< 0.001***
Incidence, per 10^6 cDDDs (95% CI)	0.05 (0.03–0.11)	0.30 (0.14–0.68)	0.03 (0.01–0.20)	-	-	

Values are presented as number (%) not otherwise specified.
ALT = alanine aminotransferase, cDDD = cumulative daily drug dose, UNL = upper normal limit (40 IU/L), CI = confidence interval, RUCAM = Roussel Uclaf Causality Assessment Method, IRR = incidence rate ratio.
[a]Reference was the losartan group.
*P < 0.05, **P < 0.01, ***P < 0.001.

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Causes and clinical manifestations of severe ALT elevation during ARB therapy

Of the 155 patients who had severe ALT elevation, 20 were also found to have RUCAM scores ≥ 6, indicating probable ARB-related DILI (**Table 3**). These included 11 (0.2%), five (0.1%), four (0.1%), and no patients in the fimasartan, candesartan, valsartan, and losartan groups, respectively ($P < 0.001$). For these cases, the median maximum ALT level was 318 IU/L (range, 206–2,394) after a median of 105 days (range, 10–861) of ARB therapy. Seventeen patients (85%) were also receiving statins, and six patients (30%) were receiving metformin. In all cases, the anti-hypertensive drug was changed to another ARB or calcium channel blocker. All cases of ARB-induced severe ALT elevation were self-limiting and recovered soon after cessation of the drug. The median time to ALT restoration (< 80 IU/L) was 27 days (range, 5–186, data not shown), but this finding was inaccurate because most repeat ALT measurements were made when patients returned for their next hospital appointment, usually 30 or 90 days after changing medications.

Of the 135 patients with severe ALT elevation but low RUCAM scores: 28 (20.7%) were related to a recent cardiovascular event such as angina, shock, or heart failure; 15 (11%) experienced postoperative transient ALT elevation; nine (6.7%) had urinary tract infections or pneumonia; nine (6.7%) were diagnosed with biliary obstruction (without radiological evidence), and seven had fatty liver (5.2%, **Supplementary Table 1**). As expected, the most common cause was DILI not related to ARB (n = 50, 37%), and we found: 13 cases related to antibiotics, 11 cases related to statins, six related to herbal supplements, three related to acetaminophen, three related to non-steroidal anti-inflammatory drugs, and 14 related to other drugs (**Supplementary Table 1**). Thus, ARB-induced liver injury should be considered as the cause of non-transient significant ALT elevation only after carefully excluding other hepatobiliary diseases, cardiovascular diseases, or infection.

Table 3. List of patients who had maximum alanine aminotransferase ≥ 200 IU/L during angiotensin-II receptor blocker therapy with high probability of drug induced liver injury (RUCAM score ≥ 6)

#	Age	Sex	ARB	Dose	Duration, days	Baseline ALT, IU/L	Peak ALT, IU/L	AST[a], IU/L	Albumin[a], g/dL	Bilirubin[a], mg/dL	ALP[a], IU/L	GGT[a], IU/L	Statin	Metformin	DM	Fatty liver	RUCAM	Department
1	62	2	Fimasartan	30	88	35	383	324	4.7	1.3	97		Y	Y	Y	N	10	IMC
2	64	1	Fimasartan	120	12	44	419	351	3.5	0.7	118		Y	Y	Y	N	10	Others
3	72	2	Fimasartan	60	48	37	2,394	1,380	3.9	1.4	268	200	Y	N	N	N	10	NR
4	35	1	Fimasartan	60	146	39	218	110	4.7	0.9	75	33	Y	N	N	Y	9	IMC
5	47	1	Fimasartan	120	337	18	631	303	4.5	1.0	93	93	Y	N	N	N	9	IMC
6	49	2	Fimasartan	120	105	37	226	82	3.8	0.5	175	327	Y	N	N	Y	9	IMN
7	66	2	Fimasartan	60	91	41	300	211	3.2	1.0	64	204	N	N	N	-	8	NR
8	42	1	Fimasartan	30	212	59	260	105	4.7	1.5	49	58	N	N	N	Y	6	IMC
9	56	2	Fimasartan	30	105	19	840	434	3.2	0.7	118		Y	N	N	N	6	IMN
10	59	1	Fimasartan	120	92	22	351	125	4.3	1.1	115		Y	Y	Y	-	6	IMC
11	77	2	Fimasartan	120	196	12	241	267	3.8	0.5	68	43	Y	N	N	N	6	IMN
12	71	2	Candesartan	8	21	39	212	221	3.8	0.5	103		Y	N	Y	N	10	IMC
13	59	2	Candesartan	8	241	24	220	159	3.9	0.8	57		Y	N	N	N	6	IMC
14	58	1	Candesartan	16	298	6	629	299	4.0	0.9	310		Y	N	Y	N	6	IMN
15	77	2	Candesartan	8	157	33	335	185	4.0	0.4	56		Y	Y	Y	-	6	IMN
16	79	2	Candesartan	8	31	86	219	53	2.8	0.7	81	44	Y	N	N	-	6	NS
17	71	2	Valsartan	80	66	46	706	866	3.3	10.4	334	363	Y	N	N	-	6	IMC
18	66	1	Valsartan	80	861	24	1,570	1,480	3.3	14.1	268	114	Y	N	N	-	7	IMC
19	78	2	Valsartan	80	360	89	248	192	4.3	0.8	91	31	N	N	Y	Y	6	IME
20	60	2	Valsartan	80	55	12	206	117	4.5	0.4	60	12	Y	Y	Y	-	7	IMC

ARB = angiotensin-II receptor blocker, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase, DM = diabetes mellitus = RUCAM = Roussel Uclaf Causality Assessment Method, Y = yes, N = no, IMC = cardiology, NR = neurology, IMN = nephrology, NS = neurologic surgery, IME = endocrinology.
[a]Data obtained the same date of maximum ALT.

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Clinical characteristics to predict clinically significant ALT elevation during ARB therapy

As shown in **Table 4**, patients with significant (> 120 IU/L) ALT elevation were younger (P < 0.001), more likely to be men (P < 0.001), and more likely also to have DM (P < 0.001). The proportion of patients taking statins was lower in the group with significant ALT elevation (P < 0.001), but more patients were taking metformin (P < 0.001) than in the group without significant ALT elevation. In the baseline laboratory findings, the elevated ALT group showed significantly higher AST, ALT, ALP, and gamma glutamyltransferase (GGT) levels than the non-elevated ALT group (P < 0.001, respectively). Moreover, glucose and TG levels were significantly higher in the elevated ALT group (P < 0.001). The characteristics of patients with and without severe (> 200 IU/L) ALT elevation were compared in **Supplementary Table 2**). Multivariable analysis showed that the ARB selected was an independent predictor of significant (> 120 IU/L) ALT elevation after adjustment for age, sex, baseline ALT, serum TG level, and statin medication use (**Table 5**). This was because the fimasartan group showed an independently higher risk of significant ALT elevation (HR, 1.9; 95% CI, 1.39–2.59; **Table 5**). Younger age and elevated baseline ALT levels were independent predictors of significant ALT elevation. The subgroup with high serum TG (≥ 150 mg/dL) had a significantly higher ALT elevation risk of 1.62 times greater than that of patients with TG levels in the normal range who were not receiving statin therapy (**Table 5**).

Table 4. Comparison of characteristics between patients with maximum ALT level > 120 and ≤ 120 IU/L

Characteristics	Total (N = 27,115)	Maximum ALT ≤ 120 IU/L (n = 26,553)	Maximum ALT > 120 IU/L (n = 562)	*P* value
Age, yr	64.6 ± 13.6	64.7 ± 13.5	60.9 ± 15.1	< 0.001***
Male	14,630 (54.0)	14,264 (53.7)	366 (65.1)	< 0.001***
Duration of medication, days	432.7 ± 516.3	432.5 ± 516.9	443.6 ± 488.1	0.614
cDDD	492.3 ± 656.8	491.9 ± 658.1	509.1 ± 591.8	0.538
Underlying co-morbidity				
Diabetes mellitus	11,111 (41.0)	10,861 (40.9)	250 (44.5)	< 0.001***
Fatty liver disease	1,852/7,683 (24.1)	1,780/7,416 (24.0)	72/267 (27.0)	0.266
Co-medication				
Statins	18,784 (69.3)	18,400 (69.3)	384 (68.3)	< 0.001***
Metformin	7,943 (29.3)	7,758 (29.2)	185 (33.0)	< 0.001***
Baseline laboratory finding				
AST, IU/L	28.0 ± 16.7	27.6 ± 14.7	44.2 ± 52.9	< 0.001***
ALT, IU/L	25.1 ± 17.3	24.7 ± 16.3	42.9 ± 37.5	< 0.001***
ALP, IU/L (n = 23,972)	80.3 ± 39.8	79.9 ± 38.9	97.2 ± 67.0	< 0.001***
Total bilirubin, mg/dL (n = 20,012)	0.73 ± 0.48	0.73 ± 0.45	0.84 ± 1.33	< 0.001***
GGT, IU/L (n = 11,798)	46.3 ± 73.5	44.5 ± 68.1	98.1 ± 154.2	< 0.001***
Glucose, mg/dL (n = 19,746)	125.6 ± 49.5	125.4 ± 49.4	133.5 ± 54.9	0.003**
HbA1c, % (n = 12,840)	6.5 ± 1.4	6.5 ± 1.4	6.4 ± 1.2	0.553
Total cholesterol, mg/dL (n = 20,005)	164.4 ± 43.4	164.5 ± 43.3	158.7 ± 48.0	0.014*
TG, mg/dL (n = 17,195)	140.8 ± 99.4	140.3 ± 98.5	163.7 ± 135.2	< 0.001***
HDL, mg/dL (n = 16,469)	49.1 ± 12.6	49.1 ± 12.6	47.9 ± 13.3	0.094
LDL, mg/dL (n = 16,384)	97.1 ± 32.2	97.1 ± 32.1	99.8 ± 37.5	0.148
Primary department of prescription[a]				< 0.001***
Cardiology	10,583 (39.0)	10,386 (98.1)	197 (1.9)	
Neurology	4,115 (15.2)	4,038 (98.1)	77 (1.9)	
Nephrology	3,190 (11.8)	3,131 (98.2)	59 (1.9)	
Endocrinology	2,710 (10.0)	2,668 (98.5)	42 (1.6)	

Values are presented as mean ± standard deviation or number (%).
cDDD = cumulative daily drug dose, AST = aspartate aminotransferase, ALT = alanine aminotransferase, ALP = alkaline phophatase, GGT = gamma glutamyltransferase, HbA1c = hemoglobin A1c, TG = triglyceride, HDL = high density lipoprotein, LDL = low density lipoprotein.
[a]Percentage is a proportion of patients who mainly prescribed the drug within each department.
*P < 0.05, **P < 0.01, ***P < 0.001.

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Table 5. Multivariable cox analysis for the development of significant ALT elevation (> 120 IU/L) during ARB therapy

Variables	HR (95% CI)	*P* value
Age	0.98 (0.98–0.99)	0.001**
Male	1.15 (0.91–1.46)	0.243
Baseline ALT	1.02 (1.01–1.02)	< 0.001***
Metformin	1.17 (0.93–1.47)	0.181
TG & statin		
TG < 150 mg/dL, statin (–)	1	
TG < 150 mg/dL, statin (+)	0.86 (0.61–1.22)	0.390
TG ≥ 150 mg/dL, statin (–)	1.62 (1.03–2.55)	0.038*
TG ≥ 150 mg/dL, statin (+)	0.96 (0.67–1.38)	0.838
Class of ARB		0.002**
Losartan	1	
Fimasartan	1.90 (1.39–2.59)	< 0.001***
Candesartan	0.91 (0.66–1.26)	0.566
Valsartan	1.19 (0.87–1.62)	0.280

ALT = alanine aminotransferase, ARB = angiotensin type II receptor blocker, HR = hazard ratio, CI = confidence interval, TG = triglyceride.
*P < 0.05, **P < 0.01, ***P < 0.001.

DISCUSSION

This study identified cases of ARB-induced ALT elevation and documented the incidence in a large multicenter cohort. Because the FDA provides safety information for every approved drug, including DILI,[15] it is expected that all ARBs approved by the FDA have been proven safe. Candesartan, valsartan, and losartan reportedly have a low rate of serum ALT elevation (< 2%).[4-6] Nonetheless, clinicians frequently encounter ALT elevation while prescribing ARBs and usually judge this to have other causes. Indeed, there were various causes for patients whose serum ALT levels are found to be significantly increased during ARB therapy. Although the incidence rates of significant and severe ALT elevation among patients taking ARB in this study were low, understanding this phenomenon can prevent chronic hepatitis progression in patients with hypertension, and avoid misdiagnoses of fatty or cryptogenic liver diseases. Interestingly, younger patients were more vulnerable to ALT elevation, and co-medication with statins did not increase the risk of elevated ALT during ARB therapy. To the best of our knowledge, this study is the first to demonstrate drug-related liver injury using a large hospital-based cohort. This suggests that prospective approaches to monitor drug-induced adverse events using CDW are promising since this method reduces the necessity of manual data collection for traditional post-marketing surveillance.

In this study, all patients with severe ALT elevation showed spontaneous improvement after drug cessation. The benign clinical course correlated to a well-known condition of transaminase elevation, also known as “transaminitis,” in which transaminase levels increase as a result of the administration of drugs such as statins.[16] In the case of statins, persistent aminotransferase elevation was found in < 1% of patients receiving an initial or intermediate dose, and in about 3.0% of those receiving a high dose, but severe hepatic failure was extremely uncommon.[16] Thus, experts recommend continuing with statin therapy if the patients are asymptomatic and have moderate ALT because the clinical course of transaminitis is benign and mild, whereas the cardiovascular benefit from statin therapy is substantial.[17] Regarding ARBs, clinicians have several alternative options if transaminitis occurs when using a particular ARB drug, and the condition can be resolved by changing to another drug.

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Although the incidence of severe ALT was not significantly different, more patients taking fimasartan experienced ALT elevation (> 2%) and possible drug-induced injury compared to the other ARBs assessed in the present study. Because of its non-renal pharmacodynamic characteristics, using fimasartan initially raised concerns about hepatic dysfunction, but previous studies showed that the long-term safety of fimasartan did not differ according to the cause of underlying liver disease.[18] Nonetheless, the significant ALT elevation rates were consistently higher in the fimasartan group in a dose-dependent manner (**Supplementary Table 3**). Moreover, 11 of the 20 patients with DILI in this study were taking fimasartan (**Table 3**). Thus, it is recommended that physicians monitor the liver function of people receiving fimasartan therapy, although the drug has excellent potency for controlling hypertension and preventing other cardiovascular diseases.

Usually, older people are thought to be more vulnerable to DILI because aging can affect the pharmacokinetics of drugs. Nevertheless, several population-based studies have shown that the increasing incidence of DILI is related to polypharmacy in older people,[19,20] and not solely associated with physiological age. In our study, significant ALT elevation during ARB therapy was associated with young age and high TG levels, which may be related to the prevalence of metabolic syndrome, although we could not clearly confirm how many metabolic syndrome patients were included owing to the lack of anthropometric data in the most subjects. Although exposure to a specific drug is critical for triggering DILI, the host factor is also crucial. Several cytochrome P450 activities (i.e., CYP1A2, 2C9, 2D6, and 2E1) have been reported to be increased in obese patients, leading to increased levels of toxic metabolites.[21] Indeed, obesity, diabetes, or multiple medications are risk factors for statin-induced liver function changes.[22,23] Moreover, acetaminophen or halothane hepatotoxicity was more common in patients with obesity or non-alcoholic fatty liver disease (NAFLD) as these conditions also lead to increased CYP2E1 activity.[21]

This study had several limitations. First, the incidence of ARB-induced ALT elevation was not calculated in a balanced group, and we selected the four most frequently prescribed drugs of all kinds of ARB in our study. Therefore, the characteristics of each ARB group were not comparable because the number of cases of ARB-induced ALT elevation was insufficient. Thus, we focused on describing all cases with various clinical characteristics in **Table 3**, allowing readers to check the clinical features in detail. Second, our study included patients with mild abnormal ALT at baseline, which can be related to metabolic syndrome (**Supplementary Table 4**). Nonetheless, the body mass index and body weight, essential components of metabolic syndrome, were not evaluated due to the CDW-based design, as most subjects did not have their weight-related records. Third, patients whose maximum ALT < 120 IU/L were not evaluated for the causality assessment, so mild ALT elevation associated with ARB would not have been detected. Moreover, the cholestatic pattern of DILI might be masked in this study population. Initially, we tried to evaluate the R ratio in all cases and describe the cholestatic pattern DILI. However, this may have led to misdiagnoses because many patients with cholestatic type LFT abnormality had suspected of having biliary disease/obstruction after the medical record review. Additionally, the RUCAM scores could not be evaluated by multiple assessors because of the privacy protection policy of the hospitals; therefore, the discordant rate could not be indicated. Nonetheless, each rater evaluated the cases based strictly on the objective criteria recommended by RUCAM. Finally, other factors, such as alcohol consumption, tobacco usage, other drug use, or dietary supplements, which were not addressed in the medical records and could not be assessed due to the retrospective design of this study, may have affected ALT.

In conclusion, approximately 2% of patients receiving ARB therapy experienced significant ALT elevation (4.24 per 10^6 cDDDs), and 0.07% (0.15 per 10^6 cDDDs) could be considered

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ARB-related DILI. Elevated ALT was more commonly seen with fimasartan than with the other ARBs, but the condition resolved after drug cessation. Clinicians should be aware of the possibility of ARB-related ALT elevation in patients with unexplained chronic abnormal ALT.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Causes of severe alanine aminotransferase elevation (> 200 IU/L) but RUCAM score < 6 during angiotensin-II receptor blocker therapy

Click here to view

Supplementary Table 2

Comparison of characteristics between patients with maximum ALT level > 200 and ≤ 200 IU/mL during angiotensin-II receptor blocker therapy

Click here to view

Supplementary Table 3

Frequencies of ALT elevation during fimasartan therapy

Click here to view

Supplementary Table 4

Comparison of characteristics between patients with baseline ALT level ≤ 40 and > 40 IU/L

Click here to view

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