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Leukotriene Receptor Antagonist Use and Dementia Risk in Patients With Asthma: A Retrospective Cohort Study

YUMI ISHIKURA[1], AYAKO MAEDA-MINAMI[1], MAIKO HOSOKAWA[1], ATSUTO ONODA[2], YOHEI KAWANO[1], TOMOMI IHARA[3], MASAO SUGAMATA[3], KEN TAKEDA[2] and YASUNARI MANO[1]

[1]*Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan;*
[2]*Faculty of Pharmaceutical Sciences, Sanyo-Onoda City University, Yamaguchi, Japan;*
[3]*Department of Pathology, Tochigi Institute of Clinical Pathology, Tochigi, Japan*

Abstract. *Background/Aim: Recent experimental studies have reported that leukotriene receptor antagonists (LTRAs) might protect against dementia. However, few clinical studies have examined this in humans. This study assessed whether the use of LTRAs can prevent the onset of dementia in humans. Patients and Methods: A large population-based retrospective cohort study was conducted using a health insurance claims database in Japan, which included patients newly diagnosed with bronchial asthma between 2006 and 2015. Each of these patients that was LTRA user was matched with a randomly selected LTRA non-user according to age, sex, and bronchial asthma diagnostic year. Results: There were 10,471 patients in both the LTRA user and the LTRA non-user group. Using Cox proportional hazards models, a significant reduction in the risk of developing dementia was observed in the LTRA user group compared to the non-user group (adjusted hazard ratio=0.42, 95% confidence interval=0.20-0.87, p=0.019). Conclusion: Our data suggest that the use of LTRAs may prevent the onset of dementia in asthmatic patients.*

With the aging of the global population, there is concern about the rapid rise in patients with dementia. According to the World Alzheimer Report 2015, it is estimated that 74.7 million people will develop dementia by 2030 and 131.5 million by 2050 (1). In order to decrease the incidence of dementia, it is important not only to treat the disease but also to prevent or delay its onset.

Correspondence to: Yasunari Mano, Ph.D., Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan. Tel: +81 4712136136, Fax: +81 471213636, e-mail: mano@rs.tus.ac.jp

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In recent years, drug repositioning, meaning the finding of new therapeutic effects from existing drugs, has become an important source of therapeutic options (2-4). In this study, we applied this approach to leukotriene receptor antagonists (LTRAs). LTRAs, such as Montelukast, are drugs that suppress allergic reactions in the body and can spread through the bronchi to prevent asthma-induced coughing attacks. They are primarily used for bronchial asthma and allergic rhinitis (5). Notably, prior studies have reported an association between LTRA use and dementia (6, 7). Marschallinger *et al*. have found that montelukast may restore the cognitive function in the brains of aged rats and may be effective in treating dementia (6). Tang *et al*. have shown both *in vivo* and *in vitro* that the cysteinyl leukotriene receptor 1 ($CysLT_1R$) is involved in amyloid-β (Aβ) protein-induced neurotoxicity and that blocking of $CysLT_1R$ with pranlukast, a $CysLT_1R$ antagonist, may be effective in treating Alzheimer's disease (7).

Since brain degeneration, the cause of dementia, occurs many years before the onset of dementia, LTRAs may have the potential to be effective not only in treating dementia but also in preventing or delaying its onset if taken before it develops. However, the findings by Tang *et al*., were obtained from studies on animal models and cells. Regarding clinical research, Grinde *et al*., have showed that montelukast might have a preventive effect on the onset of dementia using a prescription database (8); however, the association between LTRA use and the prevention of the onset of dementia remains controversial. Here, we conducted a retrospective cohort study using a large medical information database to clarify whether LTRA use prevents the onset of dementia in patients with bronchial asthma.

Patients and Methods

Data source. We used data from health insurance claims covering about 3.7 million people, provided by JMDC Inc. (Tokyo, Japan). This database has been accumulating data since 2005 and contains the

following: i) statements of inpatient and outpatient medical expenses, ii) dispensing and health check-up data, iii) demographic characteristics (*e.g.*, age and sex), iv) procedures, v) diagnoses of diseases coded by the International Classification of Disease (10th Revision, ICD-10), and vi) prescribed drugs (dose, quantity, and number of days of supply) from outpatient and inpatient care. Drugs were coded according to the Anatomical Therapeutic and Chemical (ATC) classification system of the World Health Organization (WHO). The data for each patient could be tracked in chronological order even in cases of multiple medical institutions visited. All data were anonymized.

Study population. The subjects of the study were patients newly diagnosed with bronchial asthma from January 1st, 2006 to December 31st, 2015, and aged ≥50 years at the time of diagnosis. We defined "newly diagnosed" patients as having no diagnosis of bronchial asthma for at least 6 months prior to diagnosis during the above-mentioned period. For this study, bronchial asthma was defined as having at least two outpatient claims or one or more inpatient claims for bronchial asthma. We excluded patients diagnosed with dementia prior to the diagnosis of bronchial asthma and patients who were enrolled for less than 6 months. The patients had "definite" and "suspected" diagnostic codes; those with suspected diagnostic codes were excluded.

Drug exposure data. We first identified patients who had received at least two prescriptions for LTRAs during the study period. To exclude prevalent users who had been using LTRAs for a long time, we restricted these patients to newly prescribed patients who had never been prescribed LTRAs before being diagnosed with bronchial asthma. We classified these patients as the "LTRA user group". LTRA was defined as montelukast or pranlukast, both of which are currently used in Japan. Patients using zafirlukast, a discontinued LTRA, were also excluded. In Japan, the approved dose for asthma treatment is 10 mg/day for montelukast and 450 mg/day for pranlukast. Patients who were diagnosed with dementia before the prescription of LTRAs and those who completed the follow-up before the prescription were excluded. Patients who were diagnosed with dementia between the first and second prescriptions of LTRAs were also excluded. We classified patients who had not been prescribed any LTRA during the survey period as the "LTRA non-user group". Each subject in the LTRA user group was matched with one randomly selected subject from the LTRA non-user group according to sex, age, and bronchial asthma diagnostic year to avoid the influence of confounding characteristics. After matching the subjects in the two groups 1:1, the index date was determined. The index date of the LTRA user group was the date that an LTRA was first prescribed, while the index date of the LTRA non-user group was defined as the interval between the initial bronchial asthma diagnosis and the first LTRA prescription of the corresponding subject in the LTRA user group. In the LTRA non-user group, we excluded patients diagnosed with dementia before the index date and patients whose follow-up was completed before the index date. Corresponding subjects in the LTRA user group were also excluded.

Patient characteristics. Patient characteristics included i) sex, ii) age at the index date, iii) medical history, iv) concomitant medications, and v) Charlson comorbidity index score within 6 months prior to the index date (9). Medical history was obtained using the following ICD-10 codes: i) cardiovascular disease, such as cardiac failure (ICD-10 codes I50 and J81), cardiac infarction (I21 to I23), angina pectoris (I20), other ischemic cardiac disease (I24 and I25), ii) peripheral vascular disease (I70 to I74, and I77), iii) cerebrovascular disease [transient ischemic attack (G45), ischemic cerebral infarction (I60 to I64), and other cerebrovascular diseases (I65 to I69)], iv) cancer (C00 to C97), v) hepatic disease (B18, K70.0 to K70.3, K70.9, K71, K73, K74, K76.0, B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, and I85), vi) diabetes mellitus (E10 to E14), vii) renal disease (I12, I13, N00 to N05, N07, N11, N14, N17 to N19, and Q61), viii) depression (F32, F33, and F34.1), ix) hypertension (I10 and I11), and x) hyperlipemia (E78). Concomitant medications were obtained using the following ATC codes: i) adrenergic drugs (inhaled drug; ATC code R03A), ii) glucocorticoid (R03BA), iii) anticholinergic drugs (R03BB), iv) allergy medication (R03BC), v) xanthine (R03DA), vi) systemic corticosteroid (H02), and vii) drugs that are reported to affect the risk of developing dementia, such as nonsteroidal anti-inflammatory drugs (NSAIDs; M01A), proton pump inhibitors (PPI; A02BC), and benzodiazepines (N05BA and N05CD) (10-12).

Outcomes and follow-up. The primary outcome evaluated in this study was the onset of dementia of all types (ICD-10 codes: F00–F03 and G30). This outcome was followed from the index date to the development of dementia, censoring for loss to follow-up, or the end of the observation period (December 31st, 2015), whichever came first. With regard to the type of dementia, Alzheimer's dementia (ICD-10 codes: F00 and G30) and vascular dementia (ICD-10 code: F01) were examined.

Statistical analysis. Patient characteristics between the two groups were compared using the *t*-test or Mann-Whitney *U*-test for continuous variables and χ^2 test for categorical variables. The person-year incidence of dementia for both groups was calculated. The risk of dementia in the LTRA user group compared with that in the LTRA non-user group was analyzed using Cox proportional hazards models. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated. To adjust the HR, the covariates with significant differences in the comparison of the baseline characteristics were used, and a p-Value<0.05 was considered statistically significant.

Results

Characteristics of the patients. A flowchart depicting the analytical process is shown in Figure 1. There were 52,971 patients newly diagnosed with bronchial asthma during the study period; 28,593 were classified as LTRA users and 24,378 were classified as LTRA non-users. Among them, 10,471 patients from each group were matched 1:1. The baseline characteristics of the patients are presented in Table I. The mean age of the selected patients from the two groups was 57.4 years and consisted of 10,298 men and 10,644 women. The LTRA user group had a lower frequency of prevalence of previous medical issues or severe comorbidities, such as cardiac failure, cerebrovascular disease, cancer, hepatic disease, diabetes mellitus, and renal disease, compared to the LTRA non-user group. For concomitant medications, there were significant differences

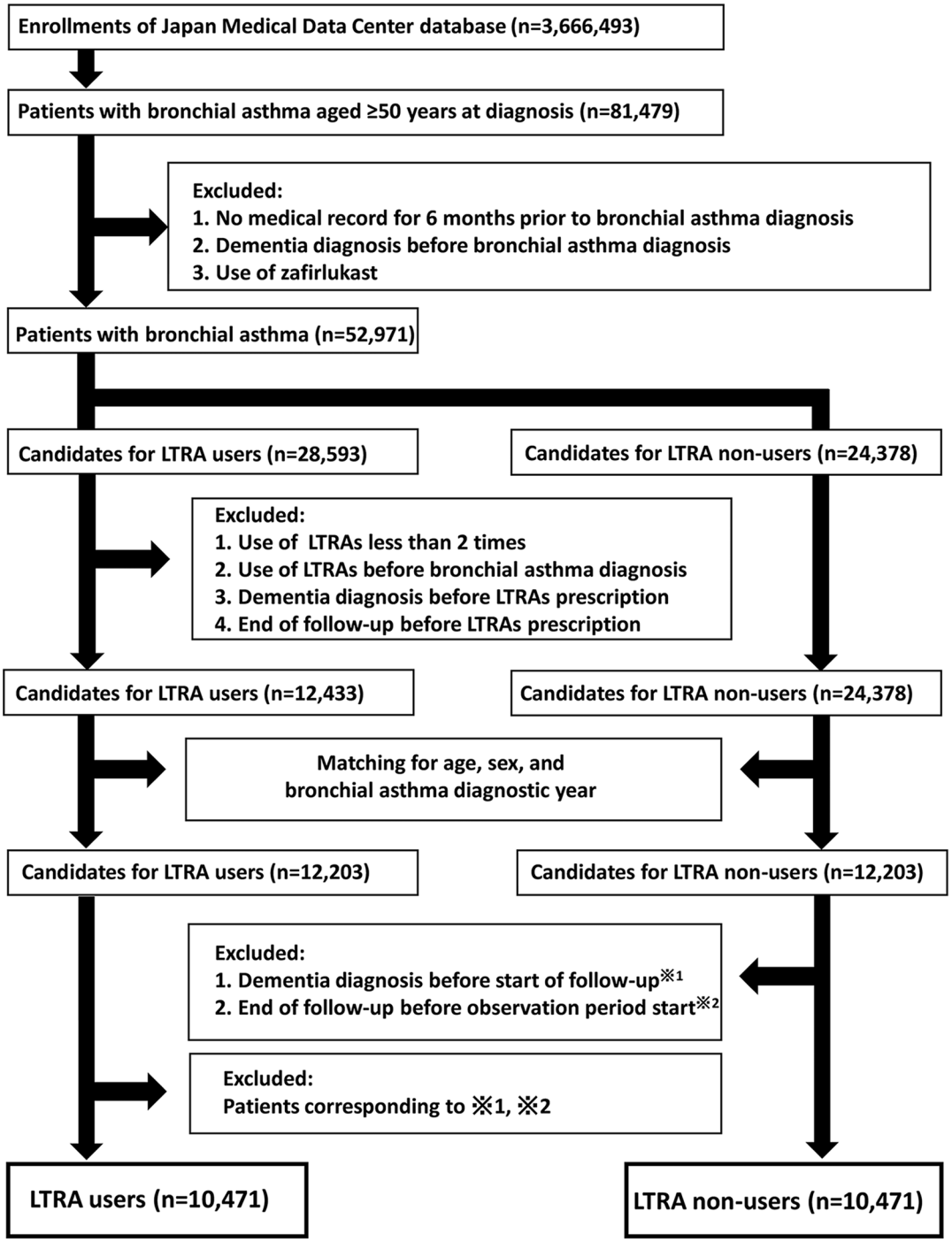

Figure 1. *Study flowchart. From the health insurance claims database we identified patients aged ≥50 years who were diagnosed with bronchial asthma. Those diagnosed with dementia or their follow-up ended prior to the start of the observation period were excluded.*

in the number of patients using bronchial asthma medications other than LTRA between the two groups. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors (PPIs), and benzodiazepines, which are known to be associated with the risk of developing dementia, among the patients, was confirmed (10-12). Of note, there was a significant difference in the number of patients using benzodiazepines between the groups.

Table I. *Baseline characteristics of the study population.*

Characteristics[1]	LTRA users (n=10,471) No. (%)		LTRA non-users (n=10,471) No. (%)		*p*-Value
Gender					
Male	5,149	(49.2)	5,149	(49.2)	1.000
Female	5,322	(50.8)	5,322	(50.8)	
Age (Mean±SD)	57.4±5.6		57.4±5.6		0.979
LTRA type[2]					
Montelukast	6,576	(62.8)			
Pranlukast	3,895	(37.2)			
Past medical history					
Cardiovascular disease	885	(8.5)	918	(8.8)	0.431
Cardiac failure	400	(3.8)	483	(4.6)	0.005**
Cardiac infarction	36	(0.3)	41	(0.4)	0.648
Angina pectoris	580	(5.5)	553	(5.3)	0.427
Other ischemic cardiac disease	108	(1.0)	116	(1.1)	0.638
Peripheral vascular disease	511	(4.9)	503	(4.8)	0.822
Cerebrovascular disease	484	(4.6)	581	(5.5)	0.003**
Transient ischemic attack	48	(0.5)	49	(0.5)	1.000
Ischemic cerebral infarction	209	(2.0)	232	(2.2)	0.290
Other cerebrovascular disease	336	(3.2)	378	(3.6)	0.119
Cancer	449	(4.3)	650	(6.2)	<0.001**
Hepatic disease	798	(7.6)	904	(8.6)	0.008**
Diabetes mellitus	1,559	(14.9)	1,744	(16.7)	<0.001**
Renal disease	222	(2.1)	282	(2.7)	0.008**
Depression	477	(4.6)	513	(4.9)	0.254
Hypertension	2,965	(28.3)	3,009	(28.7)	0.511
Hyperlipidemia	3,149	(30.1)	3,144	(30.0)	0.940
Charlson comorbidity index[3] Median (Minimum – Maximum)	1 (0-17)		1 (0-15)		0.086
Concomitant medication					
Adrenergic drug inhaled drug)	4,485	(42.8)	3,777	(36.1)	<0.001**
Glucocorticoid	799	(7.6)	1,035	(9.9)	<0.001**
Anticholinergic drug	69	(0.7)	132	(1.3)	<0.001**
Allergy medication	413	(3.9)	230	(2.2)	<0.001**
Xanthine	2,162	(20.6)	1,847	(17.6)	<0.001**
Systemic corticosteroid	3,700	(35.3)	3,073	(29.3)	<0.001**
Nonsteroidal anti-inflammatory drugs (NSAIDs)	4,634	(44.3)	4,553	(43.5)	0.265
Proton pump inhibitor (PPI)	1,337	(12.8)	1,299	(12.4)	0.441
Benzodiazepines	1,498	(14.3)	1,628	(15.5)	0.012*

*$p<0.05$, **$p<0.01$, SD: Standard deviation; LTRA: leukotriene receptor antagonist; NSAID: nonsteroidal anti-inflammatory drug. [1]Values expressed as number (%) or median (range). [2]Use of LTRAs at the index date. [3]Charlson comorbidity index is a score for evaluating comorbidities and complications. A high value indicates high severity.

Risk of developing dementia. Table II shows the association between LTRA use and the risk of developing dementia. The mean cumulative duration of LTRA administration was 70.4 days. The number of patients with an onset of dementia was 11 in the LTRA user group and 23 in the LTRA non-user group, with 9 and 15 patients with Alzheimer's dementia and 0 and 1 patients with vascular dementia, respectively. The overall incidence of dementia was 0.52 per 1,000 person-years in the LTRA user group and 1.2 per 1,000 person-years in the LTRA non-user group. After adjusting for covariates, results of the Cox proportional hazards models showed that the risk of developing dementia in the LTRA user group was significantly lower than that of the LTRA non-user group (adjusted HR=0.42, 95%CI=0.20-0.87, p=0.019).

Discussion

This retrospective cohort study showed that the use of LTRAs may be reducing the risk of developing dementia in patients with bronchial asthma.

Table II. *Multivariable Cox proportional model hazard ratios and 95% confidence intervals for the association between leukotriene receptor antagonist (LTRA) use and the risk of developing dementia among bronchial asthma patients.*

	Total of follow-up period (person-years)	No. of cases with dementia onset	Incidence rate of dementia (cases/1,000 person-years)	Unadjusted HR (95%CI)	*p*- Value	Adjusted HR* (95%CI)	*p*-Value
LTRA non-users (n=10,471)	19,360	23	1.2	1			1
LTRA users (n=10,471)	21,013	11	0.52	0.44 (0.21-0.89)	0.023	0.42 (0.20-0.87)	0.019

SD: Standard deviation; HR: hazard ratio; 95%CI: 95% confidence interval; LTRA: leukotriene receptor antagonist. *Adjusted for sex, age, cardiovascular failure, cerebrovascular disease, cancer, hepatic disease, diabetes mellitus, renal disease, adrenergic drug (inhaled drug), glucocorticoid, anticholinergic drug, allergy medication, xanthine, systemic corticosteroid, and benzodiazepine.

Recent experimental studies assessing the association between LTRAs and dementia found elevated levels of leukotrienes in patients with neurodegenerative diseases and brain injuries as well as in the aged brain. Such increases in leukotrienes may be related to neuroinflammation (13-16). When montelukast was administered to older rats, neuroinflammation was reduced and neurogenesis was promoted, possibly leading to structural and functional rejuvenation (6). This suggests that the use of LTRAs may restore cognitive function and, thus, possibly be effective at treating dementia.

Tang *et al*. have shown that $A\beta_{1\text{-}42}$ can increase the expression of $CysLT_1R$ in the hippocampus and cortex of mice and that a $CysLT_1R$ antagonist not only can reverse this upregulation but also inhibit the $A\beta_{1\text{-}42}$–triggered neurotoxicity and memory impairment. In addition, treatment with the $CysLT_1R$ antagonist, pranlukast, resulted in similar beneficial effects on memory behavior and long-term potentiation in the hippocampus to memantine or donepezil (7). Moreover, montelukast has been reported to attenuate learning and memory impairment in an experimental Alzheimer's disease mouse model (17). This suggests that $CysLT_1R$ is involved in $A\beta_{1\text{-}42}$–induced neurotoxicity and that blocking $CysLT_1R$ with a $CysLT_1R$ antagonist may be effective in treating Alzheimer's disease. Thus, there is strong evidence showing the potential effectiveness of LTRAs in treating dementia, and we speculate that they may also prevent the onset of dementia if administered early since changes in brain function and degeneration occur before the onset of dementia (18, 19). For example, the Alzheimer's disease process begins more than 20 years before the clinical onset of dementia (20). In our study we were not able to evaluate the effect of LTRAs use on the risk of developing Alzheimer's disease because of the insufficient number of cases. Further research is needed to clarify whether LTRA use can prevent the onset of Alzheimer's disease.

A previous study by Grinde *et al*. that used a prescription database also noted a preventive effect of the LTRA use on the onset of dementia (8). Compared to their study ours has several strengths. First, we used data from a large-scale, real-world population, including outpatient and inpatient hospital prescriptions, whereas the Grinde *et al*., only analyzed pharmacy prescriptions. Second, by including only new LTRA users and excluding those who had been using LTRAs for a long time, we can have more confidence in the association between the use of LTRA and the prevention of dementia. Finally, we adjusted for possible covariates that may be related to the onset of dementia, taking into account the use of NSAID, PPIs, and benzodiazepine, in addition to age and sex.

This study had several limitations. First, the average age of patients included in this study was relatively young, at 57.4 years of age. In the database used, the number of elderly people who were likely to develop dementia was small. Age is the most important risk factor for dementia; increasing age is associated with a higher incidence of dementia (21-23). The present study showed that the incidence per 1,000 person-years was 0.52 and 1.2 for the LTRA user and LTRA non-user groups, respectively. Results from a meta-analysis have shown that the incidence of age-specific dementia was 1.1 per 1,000 person-years in adults aged 60-64 (23). The incidence of age-specific dementia has also been found to be 1.28 per 1,000 person-years in adults aged 55-64 years in a Canadian study (24). In Japan, there are a few reports on such incidence estimates in persons aged around 60 years. Yamada *et al*. have reported that the age-specific incidence of dementia per 1,000 person-years is 2.0 and 3.2 for men aged 60-64 and 65-69, respectively, and 1.2 for women aged 65-69 years old (25). Although the trends differ among countries, sexes, and age groups, the dementia incidence in our study was similar to those found in other studies.

Second, the diagnosis of dementia in our study was based on the ICD-10 coding. This bears concerns about the validity

of the dementia diagnoses coding in the data. To ensure accurate diagnosis, it is important for estimation methods to have a high positive predictive value (PPV), with a high proportion of those identified as having dementia in the collected data sets of population-based studies being true dementia cases (26). In a Japanese validation study, Yamada *et al*. have reported that the PPV for dementia diagnoses by investigation using the ICD-10 code and the chart reviews as gold standard can be 100% (27). A systematic review of validation studies on ICD coding for dementia has reported that 16 of 27 eligible studies had a high PPVs of 75%-100% (26). Thus, previous studies using ICD codes have demonstrated that these are accurate for identifying dementia and other diseases.

Third, we were unable to consider factors, such as drinking and smoking, which have been reported to affect the onset of dementia (28, 29). In order to reduce bias between the groups, patients were matched and limited by their sex and age when they were first diagnosed with bronchial asthma. This allowed us to homogenize patient characteristics before the start of outcome follow-up and to adjust for available confounding factors, including concomitant medications and other comorbidities, as much as possible.

Fourth, in database studies of this kind, it is not possible to confirm whether the patients actually take their medications. This factor may have affected the cohorts since medication compliance is probably non-differentially distributed between the two groups.

In our study, the mean administration period of LTRAs was 70.4 days. Although there may be species-specific differences in the administration period and effect of LTRAs, in basic studies using either mice or rats, behavioral tests to assess memory were conducted 4-6 weeks following LTRA administration (6, 17). In this study, we could not conduct a stratified analysis to investigate the dose-response relationship between the use of LTRAs and the onset of dementia; therefore, a prospective study with a long-term administration of LTRAs is needed.

In conclusion, our results suggest that the use of LTRAs may prevent the onset of dementia in patients with bronchial asthma. Currently, drugs for the treatment of dementia are available, but preventive drugs are not. LTRAs are likely to be clinically useful as novel drugs for reducing the risk of dementia or even preventing it.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

YI, AO, KT, and YM conceived the study. YI, MH, AM analyzed the data, and YI, AM performed the statistical analysis. YI drafted the manuscript. AM, AO, YK, TI, MS, KT, and YM contributed to discussions and reviewed the final manuscript. All the Authors approved the final manuscript.

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