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Trends in prescribing montelukast in patients with asthma in real-life: Results from the Turkish adult asthma registry

Şengül Beyaz[a,b*], Münevver Erdinç[c], Serhat Hayme[d], Ayşe Feyza Aslan[b], Ömür Aydın[e], Derya Gökmen[f], Gözde Köycü Buhari[g], Zeynep Çelebi Sözener[e,a], Bilun Gemicioğlu[h], İsmet Bulut[i], Cihan Örçen[j], Seçil Kepil Özdemir[k], Metin Keren[i], Ebru Damadoğlu[l], Tuğçe Yakut[m], Ayşe Füsun Kalpaklıoğlu[n], Ayşe Baccıoğlu[n], Sümeyra Alan Yalım[n], İnsu Yılmaz[o], İlkay Koca Kalkan[g], Mehmet Atilla Uysal[p], Elif Yelda Özgün Niksarlıoğlu[p], Ali Fuat Kalyoncu[l], Gül Karakaya[l], Müge Erbay[q], Sibel Naycı[r], Fatma Merve Tepetam[i], Aslı Akkor Gelincik[b], Hülya Dirol[s], Özlem Göksel[t], Selen Karaoğlanoğlu[u], Ferda Öner Erkekol[v,w], Sacide Rana Isık[x], Füsun Yıldız[y,z], Yasemin Yavuz[f], Dilek Karadoğan[aa], Nurgül Bozkurt[s], Ümmühan Şeker[ab], İpek Kıvılcım Oğuzülgen[ac], İlknur Başyiğit[y], Serap Argun Barış[y], Elif Yılmazel Uçar[ad], Tuba Erdoğan[ae], Mehmet Polatlı[af], Dane Ediger[ag], Fatma Esra Günaydın[ag], Murat Türk[o,ah], Leyla Pür[ai], Zeynep Yeğin Katran[i], Yonca Sekibağ[h], Enes Furkan Aykaç[h], Dilşad Mungan[e], Özcan Gül[e], Ali Cengiz[e], Bülent Akkurt[k], Şeyma Özden[i], Semra Demir[b], Derya Ünal[b], Ali Can[b], Reyhan Gümüşburun[t], Gülhan Boğatekin[t], Hatice Serpil Akten[t], Sinem İnan[t], Aliye Candan Öğüş[s], Murat Kavas[i], Demet Polat Yuluğ[aj], Mehmet Erdem Çakmak[l], Saltuk Buğra Kaya[l], Gülistan Alpagat[n], Eylem Sercan Özgür[r], Oğuz Uzun[ak], Şule Taş Gülen[af], Gülseren Pekbak[ag], Deniz Kızılırmak[al], Yavuz Havlucu[al], Halil Dönmez[am], Bahar Arslan[o], Gülden Paçacı Çetin[o], Şadan Soyyiğit[v], Bilge Yılmaz Kara[aa], Gülden Paşaoğlu Karakış[an], Adile Berna Dursun[am,ao], Reşat Kendirlinan[ap], Ayşe Bilge Öztürk[aq], Can Sevinç[ar], Gökçen Ömeroğlu Şimşek[ar], Öznur Abadoğlu[as], Pamir Çerçi[at], Taşkın Yücel[au], İrfan Yorulmaz[av], Zahide Çiler Tezcaner[av], Emel Çadallı Tatar[aw], Ahmet Emre Süslü[au,ax], Serdar Özer[au], Engin Dursun[ay], Arzu Yorgancıoğlu[al], Gülfem Elif Çelik[e]

[a]*Clinic of Immunology and Allergy Diseases, Ankara Bilkent City Hospital, Ankara, Turkey*
[b]*Department of Internal Medicine, Division of Immunology and Allergy Diseases, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey*
[c]*Department of Pulmonology, Faculty of Medicine, Ege University, Izmir, Turkey*
[d]*Department of Biostatistics and Health Informatics, Erzincan Binali Yildirim University School of Medicine, Erzincan, Turkey*
[e]*Department of Chest Disease, Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey*
[f]*Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey*

***Corresponding author**: Şengül Beyaz, Clinic of Immunology and Allergy Diseases, Ankara Bilkent City Hospital, Bilkent Blv. No:1, Çankaya/Ankara, Turkey. *Email address*: sengulbeyaz@gmail.com

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[g]*Department of Immunology and Allergy, Ankara Ataturk Sanatoryum Training and Research Hospital, University of Health Sciences, Ankara, Turkey*
[h]*Department of Pulmonary Diseases, Cerrahpaşa Faculty of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey*
[i]*Department of Immunology and Allergy, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[j] *Clinic of Allergy and Immunology, Kocaeli Derince Training and Research Hospital, University of Health Sciences, Kocaeli, Turkey*
[k]*Department of Chest Diseases, Division of Allergy and Immunology, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, University of Health Sciences, Izmir, Turkey*
[l]*Department of Chest Diseases, Division of Allergy and Clinical Immunology, Hacettepe University Faculty of Medicine, Ankara, Turkey*
[m]*Clinic of Immunology and Allergic Diseases, Diyarbakir Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey*
[n]*Department of Allergy and Immunology, Faculty of Medicine, Kirikkale, Kirikkale University, Turkey*
[o]*Department of Chest Diseases, Division of Allergy and Immunology, Erciyes University School of Medicine, Kayseri, Turkey*
[p]*Department of Chest Diseases, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, University of Health Sciences, Istanbul, Turkey*
[q]*Clinic of Immunology and Allergy Diseases, Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey*
[r]*Department of Chest Diseases, Mersin University Faculty of Medicine, Mersin, Turkey*
[s]*Department of Chest Diseases, Akdeniz University Faculty of Medicine, Antalya, Turkey*
[t]*Faculty of Medicine, Pulmonary Medicine, Immunology and Allergy, Ege University, Izmir, Turkey*
[u]*Department of Pulmonology, Ordu University, Training and Research Hospital, Ordu, Turkey*
[v]*Clinic of Immunology and Allergic Diseases, Ankara Bilkent City Hospital, Ankara Yildirim Beyazit University Faculty of Medicine, Ankara, Turkey*
[w]*Division of Allergy and Immunology, Medicana International Ankara Hospital, Ankara, Turkey*
[x]*Adult Allergy and Immunology Department, American Hospital, Istanbul, Turkey*
[y]*Department of Pulmonary Diseases, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey*
[z]*Department of Pulmonary Diseases, School of Medicine, Lefkoşa, Cyprus Internatıonal Unıversıty, Cyprus*
[aa]*Department of Chest Diseases, Recep Tayyip Erdoğan University School of Medicine, Rize, Turkey*
[ab]*Clinic of Immunology and Allergic Diseases, Bursa City Hospital, Bursa, Turkey*
[ac]*Department of Pulmonary Diseases, Gazi University School of Medicine, Ankara, Turkey*
[ad]*Department of Pulmonary Disease, Ataturk University Faculty of Medicine, Erzurum, Turkey*
[ae]*Department of Internal Medicine, Division of Immunology and Allergy, Faculty of Medicine, Baskent University, Ankara, Turkey*
[af]*Department of Pulmonology, School of Medicine, Aydin Adnan Menderes University, Aydin, Turkey*
[ag]*Department of Chest Diseases, Division of Immunology and Allergy, Faculty of Medicine, Bursa Uludag University, Bursa, Turkey*
[ah]*Clinic of Immunologic and Allergic Diseases, Kayseri City Hospital, Kayseri, Turkey*
[ai]*Adult Allergy Service, Glenfield Hospital, University Hospitals of Leicester, Leicester, UK*
[aj]*Clinic of Chest Diseases, Mersin City Training and Research Hospital, Mersin, Turkey*
[ak]*Department of Pulmonary Medicine, Ondokuz Mayis University, Samsun, Turkey*
[al]*Department of Pulmonology, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey*
[am]*Department of Chest Diseases, Division of Allergy and Immunology, School of Medicine, Recep Tayyip Erdogan University, Rize, Turkey*
[an]*Department of Chest Diseases, Adult Allergy-Immunology Unit, School of Medicine, Biruni University, Istanbul, Turkey*
[ao]*Department of Respiratory Medicine, Medical School, Lokman Hekim University, Ankara, Turkey*
[ap]*Clinic of Immunology and Allergic Diseases, Izmir Ataturk Training and Research Hospital, Izmir, Turkey*
[aq]*Department of Allergy and Immunology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey*
[ar]*Department of Respiratory Diseases, School of Medicine, Dokuz Eylul University, Izmir, Turkey*
[as]*Private Immunology and Allergy Clinic, Istanbul, Turkey*
[at]*Clinic of Immunology and Allergic Diseases, Van Regional Training and Research Hospital, Van, Turkey*
[au]*Department of Ear Nose and Throat, Hacettepe University Faculty of Medicine, Ankara, Turkey*
[av]*Department of Otolaryngology-Head and Neck Surgery, Ankara University School of Medicine, Ankara, Turkey*
[aw]*Department of Otolaryngology, Etlik City Hospital, University of Health Sciences, Ankara, Turkey*
[ax]*Ahmet Emre Suslu Private Ear Nose and Throat Clinic, Ankara, Turkey*
[ay]*Department of Otorhinolaryngology, Faculty of Medicine, Lokman Hekim University, Ankara, Turkey*

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Abstract
Montelukast, a leukotriene receptor antagonist (LTRA) approved for the treatment of asthma and allergic rhinitis, is widely used, though real-world data on its application in asthma management remain limited. This registry-based study evaluated the use of montelukast in adult asthma patients, examining demographic and disease characteristics, asthma control status, asthma phenotypes, presence of atopy, and treatment regimens. Among 2053 patients analyzed, 61.76% (n = 1268; mean age: 46.2 ± 14.3 years), predominantly females (~76%), received montelukast. Montelukast users showed higher rates of allergic rhinitis (P < 0.001), hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) (P = 0.008), and chronic rhinosinusitis (P = 0.008). Montelukast group also had higher atopy and total IgE levels and tended to be more eosinophilic. Montelukast was commonly preferred in allergic, eosinophilic, NSAID-exacerbated respiratory disease, and severe asthma phenotypes (P < 0.001). Patients receiving Steps 4 and 5 treatments are more likely to be prescribed montelukast (P < 0.001). Montelukast usage was higher among patients with uncontrolled asthma [ACT< 20 (OR:1.29, 95%CI:1.052–1.582, P = 0.014)]. In addition, logistic regression analyses identified the main factors associated with increased montelukast use as; female gender (OR:1.33, 95%CI:1.041–1.713, P = 0.02), presence of atopy (OR:1.46, 95%CI:1.157–1.864, P = 0.002), comorbid allergic rhinitis (OR:2.12, 95%CI:1.679–2.293, P < 0.001), and severe asthma (OR:2.18, 95%CI:1.712–2.784, P < 0.001). These findings reveal that montelukast use is prevalent among asthma patients, particularly in females, middle-aged adults, and those with comorbid allergic rhinitis, uncontrolled asthma, or specific asthma phenotypes, underscoring the factors that influence its prescription in asthma management.

Introduction

Asthma is a common, chronic, inflammatory respiratory disease.[1,2] Multiple cell types including mast cells, T-helper cells (Th2, Th17, Th1), B-cells, eosinophils, dendritic cells, and neutrophils, as well as structural bronchial cells including epithelial cells, myofibroblasts, and smooth muscle cells, drive the airway inflammation in asthma.[3] Cysteinyl leukotrienes (CysLTs) have a significant role in the pathogenesis of several diseases, with asthma being especially noteworthy.[4] CysLTs, mainly produced by mucosal mast cells, basophils, and also eosinophils are arachidonic acid-derived inflammatory lipid mediators and include leukotriene (LT) C4, LTD4, and LTE4.[5-7] Activation of CysLTs causes smooth muscle contraction, increased capillary permeability resulting in edema, an increase in mucus secretion with impaired mucociliary clearance, and leukocytes to be attracted to the airway, thereby amplifying the inflammatory response.[6] CysLTs act via CySLTR1 and CySLTR2 receptors.[8] Eosinophils, basophils, mast cells, macrophages, and smooth muscle cells express CySLTR2, whereas mast cells, neutrophils, dendritic cells, eosinophils, basophils, epithelial/endothelial cells, airway smooth muscle cells, and monocytes or macrophages express CySLTR1.[8,9]

Antileukotriene drugs namely montelukast, pranlukast, and zafirlukast are the three leukotriene receptor antagonists (LTRAs) that reduce CysLT-induced bronchoconstriction and inflammation, and are recommended for the treatment of asthma since the late 1990s.[10] They are known to be potent, selective, and competitive antagonists to the CysLTR1 receptor, with montelukast exhibiting the highest binding affinity.[11,12] Montelukast reduces leukotriene-induced airway edema, smooth muscle contraction, and cellular activity without agonist activity.[13] Throughout the progression of asthma guidelines, LTRAs were first suggested as a potential therapeutic option for individuals with mild persistent asthma, particularly in cases where there were undesirable side effects associated with inhaled corticosteroids (ICSs) or inadequate response to ICSs. Subsequently, the addition of LTRAs to low-dose ICS/long-acting beta-agonists (LABA) was also placed in the guidelines. Recent studies also suggested that people who have certain phenotypes of asthma including exercise-induced asthma, asthma associated with allergic rhinitis, asthma in obese patients, asthma in smokers, aspirin-induced asthma, elderly asthma, and cough variant asthma would have a favorable response to LTRAs.[14-16] In addition, oral administration seems to be an advantage of LTRAs.[14] However, from a general point of view, as LTRAs are considered an alternative treatment in asthma guidelines, it is not well known how LTRAs find a place for themselves in real-life conditions.

Montelukast is the LTRA agent that has been licensed for use in the treatment of asthma in our country since 1998. So far, we have no data on the use of montelukast in daily practice or the conditions in which this drug was preferred among asthma patients in our country. Recently, we published the results from a national asthma database in which 36 centers participated and many aspects of asthma were investigated in detail in order to provide national data.[17] In this study, a sub-analysis of data regarding LTRA usage by asthma specialists in secondary and tertiary care clinics in our country was conducted. Therefore, by performing these analyses, we mainly aimed to determine

when montelukast is used in treating asthma, secondarily to identify the clinical outcomes of montelukast.

Materials and Methods

Study design and the patients

This was a registry study that focused on adult asthmatic individuals who were treated with or without montelukast and were included in the Turkish Adult Asthma Registry (TAAR) which was performed between March 15, 2018 and March 15, 2022. This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee (16-10l I-I7/2017), and written informed consent was collected from all study participants. A pooled patient data from seven regions and 36 centers were included. A thorough description of TAAR's features may be found in a framework paper that has already been published.[17]

Study parameters

The detailed clinical questionnaire administered to the study participants was recorded in a web-based database and was used as a data source in our study. The patients were divided into two groups montelukast users and non-users. Then details regarding the patients' disease characteristics such as asthma attack rate, asthma control status, asthma phenotypes, presence of atopy, biomarkers (e.g., IgE and eosinophils), lung function test results, and treatment regimens, as well as demographic and clinical characteristics, were analyzed in those groups.

Asthma control

The asthma control test (ACT), which measured symptom control for the preceding four weeks, was used to measure asthma control.[1] ACT scores between 20 and 25 were classified as well-controlled asthma, scores between 16 and 19 as not well-controlled, and those between 5 and 15 were classified as very poorly controlled asthma. Furthermore, the number of asthma attacks requiring at least 3 days of oral corticosteroids (OCS) and asthma-related hospitalizations were used to assess asthma control over the previous year. Asthma-related emergency department admissions, ICU admissions, and scheduled or unscheduled physician visits were also evaluated. In addition, the patients' treatment steps were determined using GINA.

Atopy

A positive result in the skin prick test (SPT) (a standardized inhalant allergen panel, ALK/Allergo Pharma, Reinbek, Germany) or a measurement of serum-specific immunoglobulin (Ig) E (ImmunoCAP System, Phadia AB) was considered to be indicative of atopy.

Eosinophilia

A peripheral blood eosinophil count of more than 150 cells/mL, at least within the previous year or during the assessment was considered eosinophilia,

Definition of phenotypes

Individuals with clinically relevant positive skin tests or sIgE values were diagnosed with "allergic asthma." A peripheral blood eosinophil count of more than 150 cells/mL, at least within the previous year or during the assessment, was considered to be indicative of "eosinophilic asthma." "Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD)" was defined as having at least two confirmed reactions (respiratory symptoms) after receiving aspirin or other NSAIDs. "Early onset asthma" is defined as occurring before the age of 12. "Late-onset asthma" also known as adult-onset asthma, occurs when a person acquires the disease as an adult. Patients 65 years and older were assessed as the "advanced-age asthma." Patients with a BMI ≥ 30 kg/m^2 were classified as having an "obese asthma" phenotype. A post-bronchodilator FEV1/FVC level of less than 70% and the existence of clinical symptoms consistent with both asthma and COPD were considered indicators of "ACO." Patients who were uncontrolled under high-dose ICS/LABA treatment despite optimal control of all risk factors such as comorbidities, triggers, or technical noncompliance/treatment noncompliance or who required high doses of ICS/LABA to prevent it from becoming uncontrolled, or who received biologic agents/OCS in treatment were classified as "severe asthmatics."

Statistics

IBM SPSS 25.0 software package (SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses. The assumption of normal distribution was assessed using the Kolmogorov-Smirnov test, and the homogeneity of variances was evaluated using the Levene test. Descriptive statistics are displayed as mean ± standard deviation (SD) or median (minimum-maximum) for numerical variables and frequency and percentages (%) for categorical variables. For comparing categorical parameters, the chi-square test and Fisher's Exact test were performed. To compare normally or non-normally distributed continuous variables, respectively, the Independent Samples T-test or Mann-Whitney U test was used. For assessing differences between three or more groups, ANOVA or Kruskal Wallis tests were used. Tukey and Dunn Bonferonni tests were used for multiple comparisons. Univariate and Multivariable Logistic regression analysis was used to evaluate the association between variables and an odds ratio with a 95% confidence interval (CI) was given. The criteria for the variables to be included in the multivariable logistic model were determined by considering their clinical and statistical significance. P-values less than 0.05 were considered significant.

Results

Demographic and clinical features

The data of 2053 individuals whose information was recorded in the national adult asthma database were evaluated in this study. Of these patients, 1268 (61.76%) were

receiving montelukast. The proportion of female patients using montelukast was greater than that of male patients (P = 0.010) (Table 1). Patients were divided into three age groups, the 40–60 age group had significantly higher montelukast usage than the other two groups (P = 0.031) (Table 1). No significant difference was found between the groups who used and did not use montelukast in terms of BMI, place of birth, living place, education levels, occupation, and other systemic comorbidities (P > 0.05) (Table 1). The number of never-smokers using montelukast was higher than the other groups (P = 0.005) (Table 1).

The group receiving montelukast had a higher rate of concomitant allergic rhinitis (P < 0.001), hypersensitivity to NSAIDs (P = 0.008), and chronic rhinosinusitis (without nasal polyps) (P = 0.008) (Table 1). The number of patients with moderate to severe persistent rhinitis was higher in the group using montelukast than in the group not using montelukast (211 [38.1%] vs 69 [28.9%], P = 0.031). While the number of patients who did not use montelukast was higher in the group with asthma onset at age ≥65 (P = 0.001) (Table 1). The mean age of asthma onset was significantly lower in the group receiving montelukast (P = 0.007) (Table 1). T. IgE levels were higher in the montelukast group (P = 0.004), and eosinophil levels also tended to be higher in this group, but there was no significant difference (Table 1). There were no differences in FEV1 and FEV1/FVC values between the groups (Table 1). The montelukast group had a higher sensitivity rate to all allergens except molds than the group not receiving montelukast (Table 1).

Utilizing montelukast in the stepwise treatment

The current treatment steps of the patients were investigated. At GINA Steps 1–3, the majority of patients did not use montelukast (9.8% vs 2%, 11.6% vs 6%, and 33.8% vs 23.7%, respectively), whereas, at Steps 4 (19.8% vs 27.6%) and 5 (25% vs 40.6%), the majority of patients did use montelukast (Figure 1). The patients were then divided into three groups: Steps 1 and 2 (Group 1), Steps 3 and 4 (Group 2), and 5 (Group 3). In Group 1, there were a greater number of patients who did not use montelukast than those who did (n = 122 [21.4%] vs n = 87 [8.1%], p = 0.001). Similarly, the percentage of patients not receiving montelukast was higher in Group 2 (n = 306 [53.6%] vs n = 554 [1.3%], P < 0.001). In contrast, there was a significantly greater number of patients receiving montelukast in Group 3 (n = 143 [25%] vs 439 [40.6%], P < 0.001). As expected, low-dose ICS use was higher in the montelukast nonuser group (n = 132 [55.2%] vs n = 107 [44.8%]), while medium (n = 150 [33.5%]vs n = 298 [66.5%]) and high-dose (n = 94 [27.7%] vs n = 245 [72.3%]) (P < 0.001) ICS use was higher in the montelukast user group.

The patients were also examined in terms of the treatments they received, and there was no difference between the groups using montelukast and those not using it in terms of MART (n = 264 [41.4%] vs n = 168 [46.1%]) and fixed-dose conventional and reliever medication (n = 379 [59.5%] vs n = 198 [54.3%]) (P = 0.172). The most commonly used inhaled corticosteroid was budesonide in both groups (Figure 2). Fluticasone and budesonide usage were higher in the montelukast group (P = 0.001 and P = 0.038, respectively) (Figure 2). Similarly, the use of LAMA, AIT, omalizumab, and oral corticosteroids was higher in the group using montelukast compared to the nonuser group (P = 0.021, P < 0.001, P < 0.001, and P = 0.003, respectively) (Figure 2).

Furthermore, according to the treatment steps, results such as the number of asthma attacks requiring at least 3 days of corticosteroid use, the number of asthma attacks requiring less than 3 days of corticosteroid use, the number of asthma-related emergency department admissions, the number of hospital/intensive care unit admissions due to asthma, and the number of planned or unplanned doctor visits were compared between patients using and not using montelukast groups. In Step 5, the rate of patients with asthma attacks requiring at least 3 days of systemic steroids in the last 1 year was higher in the group using montelukast (P = 0.002) (Table 2). Similarly, in Steps 4 and 5, the rate of patients who had unscheduled visits due to asthma in the last 1 year was higher in the group using montelukast (P = 0.009 and P = 0.014, respectively) (Table 2).

Utilizing montelukast in different asthma phenotypes

The patients were then evaluated for whether there was a relationship between montelukast use and asthma phenotypes. It was observed that the use of montelukast was more preferred in eosinophilic asthma (n = 398 [51%] vs n = 772 [60.9%], P < 0.001), NERD (n = 69 [8.8%] vs n = 179 [14.1%], p < 0.001), allergic asthma (n = 344 [55.7%] vs n = 811 [70.5%], P < 0.001], and severe asthma (n = 165 (21.1%) vs n = 503 (39.7%), P < 0.001) phenotypes. However, it was less preferred in the nonallergic asthma phenotype (n = 281 [36%] vs n = 291 [22.9%], P < 0.001). Besides, a similar utilization pattern was observed in phenotypes such as ACO (n = 25 [3.2%] vs n = 51 [4%], P = 0.34), obese asthma (n = 235 [30.1%] vs n = 401 [31.6%], P = 0.46), early-onset asthma (n = 70 [9%] vs n = 106 [8.4%], P = 0.63), late-onset asthma (n = 92 [11.8%] vs n = 166 [13.1%], P = 0.38), and advanced age asthma (n = 14 [1.8%] vs n = 28 [2.2%], P = 0.51).

Assessment based on the status of asthma control

When asthma control status was assessed, the rate of very poorly controlled and not well-controlled patients was higher in the montelukast group (17.1% vs 22.2% and 20% vs 21.1%, respectively), whereas the rate of well-controlled patients (62.8% vs 56.7%) was higher in the non-montelukast group (Table 3). In addition, the scores of the patients in the montelukast group were lower in the evaluation of 4-week asthma symptom control with ACT scores (20 points vs 23 points, P < 0.001) (Table 3). The number of patients with asthma attacks requiring systemic steroid use for at least 3 days in the last year, the number of patients admitted to the emergency department due to asthma in the last year, and the number of patients who had unscheduled doctor visits due to asthma in the last year were higher in the montelukast group (P < 0.001) (Table 3).

Next, patients' asthma control status was classified as controlled (ACT ≥ 20 points) or uncontrolled (ACT <

Table 1 Demographic and disease characteristics of asthma patients treated with or without montelukast.

Variable	Not receiving montelukast	Receiving montelukast	P
Sex (Female/Male), n (%)	559 (71.6%)/222 (28.4%)	972 (76.7%)/296 (23.3%)	**0.010**
Age (year) (mean + SD)	47.5 ± 15.5	46.2 ± 14.3	0.056
Age groups, n (%)			
18–39 years	239 (30.9%)	399 (31.8%)	**0.031**
40–60 years	370 (47.8%)	647 (51.5%)	
>60 years	165 (21.3%)	210 (16.7%)	
BMI (kg/m^2), n (%)			
Obese (≥30)	231 (32%)	387 (32.4%)	0.746
Overweight (25–29.99)	252 (35%)	440 (36.8%)	
Normal (18.50–24.99)	220 (30.5%)	348 (29.1%)	
Lean (≤18.49)	18 (2.5%)	20 (1.7%)	
Place of birth, n (%)			
Urban	404 (56.3%)	729 (60%)	0.103
Rural	314 (43.7%)	485 (40%)	
Living place, n (%)			
Urban	686 (93.6%)	1164 (94.3%)	0.503
Rural	47 (6.4%)	70 (5.7%)	
Education, n (%)			
No school, no literate	36 (5.1%)	47 (3.9%)	0.338
Literate/Primary school	275 (38.8%)	521 (43.1%)	
High school	170 (24%)	278 (23.1%)	
College/University	228 (32.2%)	359 (29.9%)	
Occupation, n (%)			
Government officer	100 (13.9%)	177 (14.3%)	0.190
Self-employment	101 (14.1%)	154 (12.6%)	
Housewife	273 (38%)	522 (42.9%)	
Student	56 (7.8%)	91 (7.5%)	
Retired	80 (11.1%)	109 (8.9%)	
Not working	31 (4.3%)	62 (5.1%)	
Other	77 (10.7%)	104 (8.5%)	
Smoking status, n (%)			
Current smoker	105 (14%)	123 (9.9%)	**0.005**
Ex-smoker	163 (21.7%)	247 (19.8%)	
Never-smoker	482 (64.3%)	878 (70.4%)	
Allergic comorbidities, n (%)			
Allergic rhinitis	380 (52.2%)	873 (71.6%)	**<0.001**
NSAID hypersensitivity	67 (9.6%)	160 (13.7%)	**0.008**
Atopic dermatitis	36 (5.2%)	46 (4%)	0.219
Urticaria	49 (7.0%)	111 (9.5%)	0.065
Allergic contact dermatitis	14 (3.6%)	9 (1.3%)	**0.013**
Chronic rhinosinusitis (without nasal polyps)	199 (28.5%)	402 (34.4%)	**0.008**
Chronic rhinosinusitis with nasal polyp	127 (17.9%)	251 (21.1%)	0.093
Other systemic comorbidities, n (%)			
COPD	16 (2.3%)	17 (1.5%)	0.184
Diabetes mellitus	100 (14.3%)	154 (13.1%)	0.470
Thyroid diseases	116 (16.6%)	170 (14.4%)	0.212
Coronary artery disorders	124 (17.4%)	234 (19.6%)	0.237
Hypertension	123 (15.6%)	237 (18.7)	0.089
GERD	175 (25%)	322 (27.3%)	0.269
OSAS	21 (3%)	49 (4.2%)	0.199
Psychiatric disorders	56 (8%)	86 (7.3%)	0.577
Bronchiectasis	13 (1.9%)	26 (2.3%)	0.591
Age of disease onset categories, n (%)			
0–12 years	54 (8%)	102 (8.6%)	0.650
13–18 years	49 (7.1%)	97 (8.1%)	0.389
19–39 years	307 (45.4%)	591 (49.8%)	0.069
40–64 years	244 (36.1%)	385 (32.5%)	0.108
≥65 years	21 (3.1%)	12 (1%)	**0.001**

(continues)

Table 1 Continued.

Variable	Not receiving montelukast	Receiving montelukast	P
Symptom duration (year) (mean ± SD)	12.40 ± 10.12	13.31 ± 10.45	0.058
Age of disease onset (year) (mean ± SD)	34.89 ± 15.43	32.77 ± 14.19	**0.007**
Presence of atopy, n (%)			
House dust mites	241 (39.8%)	639 (56.6%)	**<0.001**
Pollens	144 (24%)	329 (29.7%)	**0.034**
Cockroaches	37 (6.3%)	107 (9.8%)	**0.028**
Molds	48 (8.2%)	117 (10.7%)	0.138
Cat dander	54 (9.1%)	113 (10.4%)	**<0.001**
Dog dander	39 (6.6%)	79 (7.3%)	**<0.001**
FEV1 (L) (Mean ± SD)	2.32 ± 0.85	2.30 ± 0.83	0.676
FEV1 (%) (Mean ± SD)	82.83 ± 19.80	81.69 ± 20.68	0.183
FVC (L) (Mean ± SD)	3.07 ± 1.07	3.00 ± 0.99	0.407
FVC (%) (Mean ± SD)	92.15 ± 18.52	90.50 ± 19.68	**0.037**
FEV1/FVC (%) (Mean ± SD)	75.67 ± 11.47	76.36 ± 11.91	0.278
Eosinophil count (cell/L) (Median, min-max)	270 (0–4800)	290 (0–3790)	0.986
Total IgE (IU/mL), (Median, min-max)	137 (2–7850)	167.50 (0–4280)	**0.004**

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, Forced expiratory volume in the first second; FVC, Forced vital capacity; GERD, gastroesophageal reflux disease; Ig, Immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug; OSAS, obstructive sleep apnea syndrome; SD, standard deviation.
Values are presented as mean ± SD, median (min-max), or number (%).

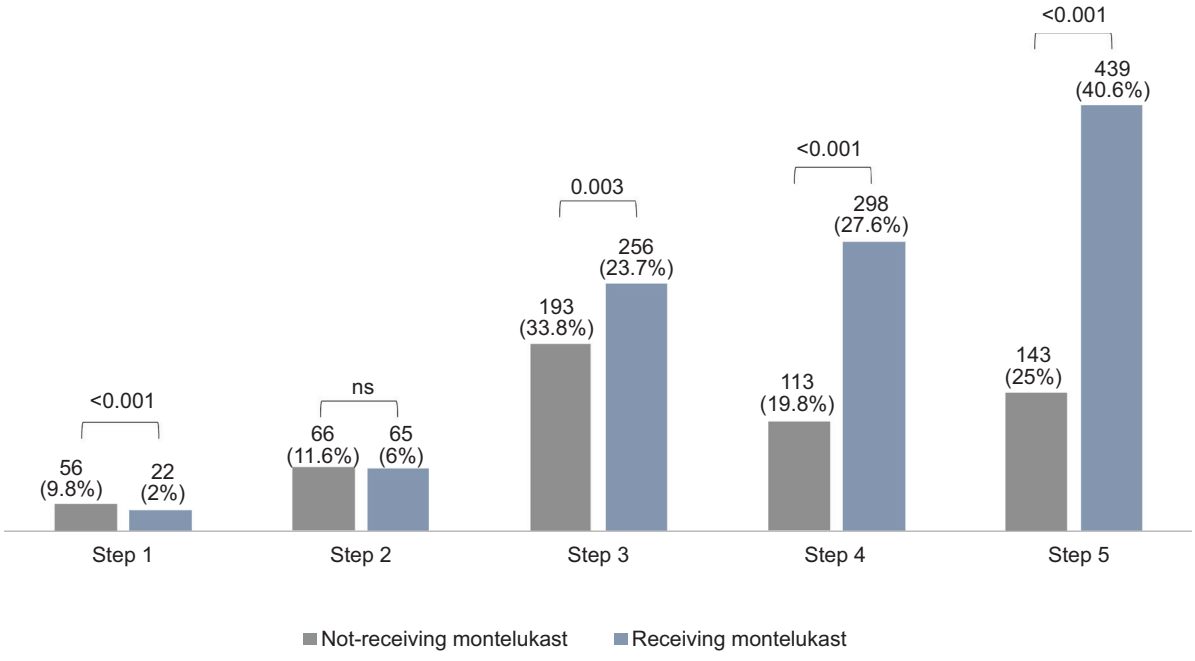

Figure 1 Treatment steps of study groups. Values are expressed as number (n) and percentage (%). P values > 0.05 are presented as NS (not significant).

20 points). It was observed that the group not receiving montelukast had a higher rate of patients with ACT ≥ 20 than the group receiving montelukast (n = 389, 62.8% vs n = 590, 56.7%), while the group receiving montelukast had a higher rate of patients with ACT < 20 (n = 230, 37.2% vs n = 450, 43.3%) (P = 0.01). And the association between asthma control status categorization and treatment status, it was observed that montelukast usage was higher in patients with ACT < 20 (OR: 1.29, 95%CI: 1.052–1.582, P = 0.014). There was no significant difference in the treatment

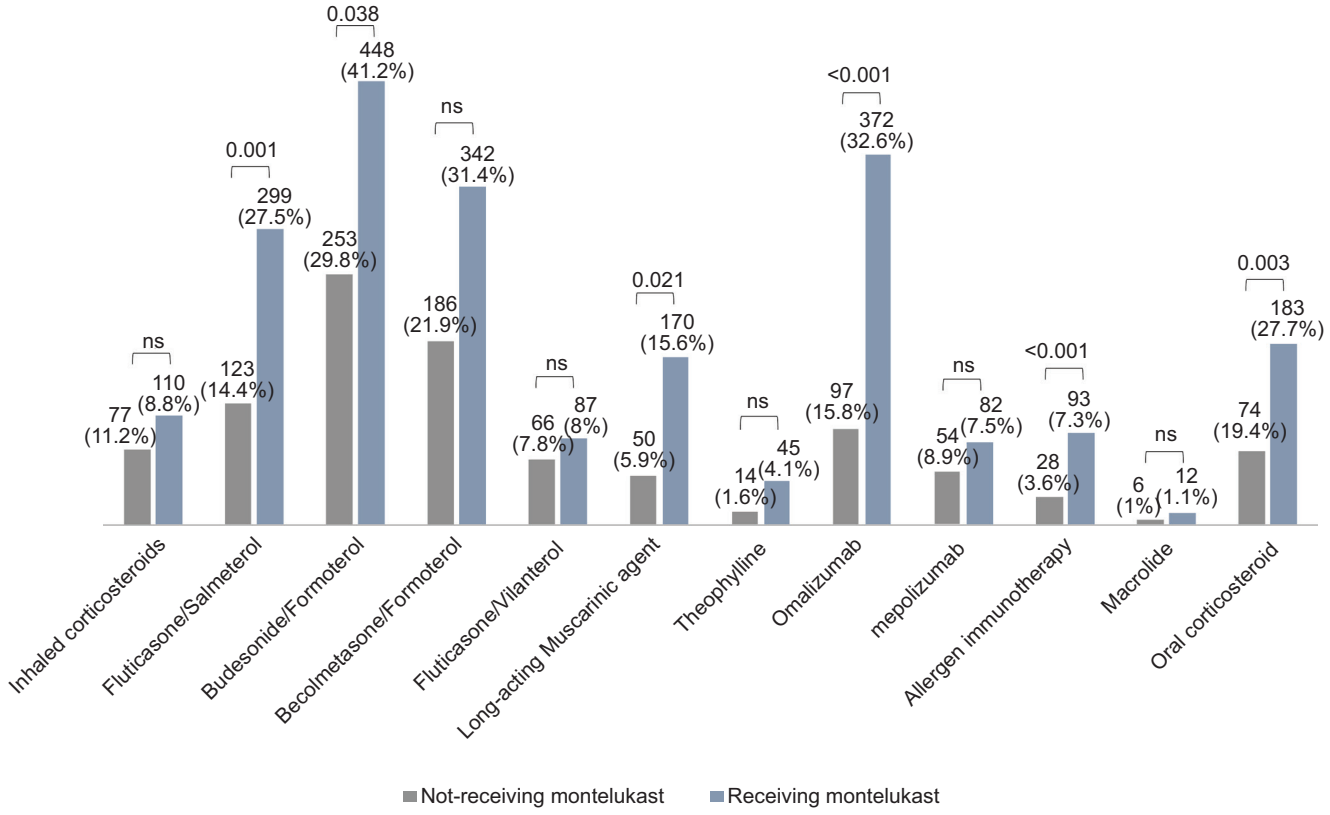

Figure 2 Evaluation of the medication utilized by the study population. Values are expressed as number (n) and percentage (%). P values >0.05 are presented as NS (not significant).

Table 2 Assessment of clinical parameters based on the treatment steps of montelukast users and nonusers.

Features		Step 1	Step 2	Step 3	Step 4	Step 5
Number of patients with asthma attacks requiring at least 3 days of systemic steroid in the last 1 year, n (%)	**Not-receiving montelukast**	1 (2.1%)	7 (12.5%)	16 (9.9%)	17 (17.2%)	40 (29.8%)
	Receiving montelukast	0	4 (7.5%)	15 (7.5%)	64 (24.3%)	195 (46.9%)
	p	NA	0.196	0.334	0.246	**0.002**
Number of patients admitted to the emergency department due to asthma in the last 1 year, n (%)	**Not-receiving montelukast**	1 (2.1%)	9 (16.1%)	26 (15.8%)	19 (19 %)	44 (33.6%)
	Receiving montelukast	1 (5%)	12 (22.3%)	29 (14.4%)	79 (30.2%)	171 (41.3%)
	p	NA	0.380	0.478	0.072	0.282
Number of patients who required hospitalization due to asthma in the last 1 year, n (%)	**Not-receiving montelukast**	1 (2.1%)	4 (7.2%)	6 (3.7%)	6 (6.3%)	12 (9.4%)
	Receiving montelukast	0	3 (5.7%)	4 (2%)	21 (8.3%)	53 (13.2%)
	p	NA	1	0.615	0.141	0.505
Patients who had unscheduled visits due to asthma in the last 1 year, n (%)	**Not-receiving montelukast**	4 (8.4%)	12 (21.4%)	30 (18 %)	20 (20.9%)	40 (30.3%)
	Receiving montelukast	0	17 (30.4%)	38 (18.6%)	99 (37.6%)	180 (43.6%)
	p	0.413	0.552	0.986	**0.009**	**0.014**

NA, not applicable.
Values are presented as number and percentage (%).

Table 3 Evaluation of the asthma control status of the study group.

Variable	Not receiving montelukast	Receiving montelukast	P
Number of patients with asthma attacks requiring at least 3 days of systemic steroid in the last 1 year, n (%)	57 (8.9%)	131 (11.7%)	**<0.001**
1 episode	56 (8.8%)	187 (16.6%)	
≥2 episodes			
Number of patients admitted to the emergency department due to asthma in the last year, n (%)	60 (9.1%)	111 (9.9%)	**<0.001**
1 episode	83 (12.9%)	228 (20.3%)	
≥2 episodes			
Number of patients who required hospitalization due to asthma in the last year, n (%)	30 (4.8%)	72 (6.5%)	0.331
1 episode	17 (2.7%)	31 (2.8%)	
≥2 episodes			
Patients who had unscheduled visits due to asthma in the last year, n (%)			
1 episode	62 (9.6%)	123 (11%)	**<0.001**
≥2 episodes	83 (12.8%)	255 (22.7%)	
Asthma control categories, n (%)			
Well-controlled (20-25 points)	389 (62.8%)	590 (56.7%)	**0.022**
Not well-controlled (16-19 points)	124 (20%)	219 (21.1%)	
Very poorly controlled (5-15 points)	106 (17.1%)	231 (22.2%)	
Asthma control test scores, median (min-max)	23 (5-25)	20 (6-25)	**<0.001**

Values are presented as number (n) and percentage (%).

Table 4 Results of the univariate and the multivariable logistic regression analysis in patients utilizing montelukast.

	Univariate			Multivariable		
	OR	95% CI	P	OR	95% CI	P
Female Gender	1.304	1.065-1.597	0.010	1.336	1.041-1.713	**0.023**
Age groups						
18-39 years	1.312	1.012-1.700	0.040	-	-	-
40-60 years	1.374	1.080-1.748	0.010	-	-	-
Allergic comorbidities						
Allergic rhinitis	2.304	1.903-2.790	<0.001	2.127	1.679-2.293	**<0.001**
NSAID hypersensitivity	1.499	1.108-2.028	0.009	-	-	-
Chronic rhinosinusitis	1.315	1.073-1.613	0.008	-	-	-
Presence of atopy	1.900	1.551-2.328	<0.001	1.469	1.157-1.864	**0.002**
Phenotypes						
Eosinophilic asthma	1.498	1.251-1.793	<0.001	-	-	-
NERD	1.696	1.265-2.274	<0.001	-	-	-
Allergic asthma	1.900	1.551-2.328	<0.001	-	-	-
Severe asthma	2.455	1.999-3.014	<0.001	2.182	1.712-2.784	**<0.001**

NERD, NSAID-exacerbated respiratory disease; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

steps of the patients according to asthma control categories (Table S1).

Results of the logistic regression analysis

Univariate and multivariable logistic regression analyses were performed to predict which variables were associated with increased montelukast use in patients with asthma. According to these analyses, the primary factors associated with increased montelukast use were identified as follows: female gender (1.3 times more likelihood, P = 0.02), presence of atopy (1.5 times more likelihood, P = 0.002), comorbid allergic rhinitis (2.1 times more likelihood, P < 0.001), and a severe asthma phenotype (2.2 times more likelihood, P = 0.002) (Table 4).

Discussion

This is the first nationwide real-life study to report the utilization of montelukast in adult patients with asthma which reviews data from the TAAR, a standardized database study. It has been documented that montelukast is preferred in the treatment of approximately 62% of patients. Certain groups such as females, those with allergic rhinitis, those with NSAID hypersensitivity, and those with chronic rhinosinusitis without nasal polyps were more likely to be prescribed montelukast. Furthermore, patients with younger asthma onset age, those in the middle age group, and those with lower asthma control scores were observed to take montelukast more often. The montelukast group had higher atopy rates. Specifically, in NERD, eosinophilic, allergic, and severe asthma phenotypes, a greater proportion of patients used montelukast than did not. Notably, montelukast prescriptions are more common among patients with uncontrolled asthma and those undergoing treatment steps 4 and 5.

In particular, in this study, we observed that a significant number of adult asthma cases in our country were using montelukast and the prevalence rate was 62%. The use of anti-leukotrienes shows different patterns among countries. Consistent with our findings, LTRAs were preferred in 57.6% of pediatric asthma cases and 75.8% of adult severe asthma patients in South Korea, whereas montelukast was utilized in only 18.9% of pediatric asthma cases in Australia.[18,19] In Sweden, LTRAs were used in 15% of patients with mild to moderate asthma and 39% of patients with severe asthma.[20] In Norway, these figures were 14% for mild to moderate asthma patients and 28% for severe asthma patients.[20] In Finland, LTRAs were used in 18% of patients with mild to moderate asthma and 44% of those with severe asthma.[20] Our findings indicate specifically, that our mild to moderate asthma patients used montelukast at a rate approximately three to four times higher (59.4%) than the corresponding LTRA usage in Sweden, Norway, and Finland. For severe asthma patients, montelukast usage in our results was similarly higher (40.6%) than the LTRA usage in Sweden and Norway, and slightly lower than in Finland and Korea.[19,20] Again, a nationwide study showed that the number of montelukast users (point prevalence) has increased over the years, rising from 0.9 per 1000 people in 1998 to 3.3 per 1000 people in 2016.[21] The use of LTRAs in the UK is more common in Steps 3, 4, or 5 of the British Thoracic Society's asthma management guidelines, which suggests they are not the first line of treatment for adult patients' initial therapy.[22,23] In the GINA, LTRAs are also recommended as either monotherapy or as an add-on to ICS in different severity levels of asthma.[1] LTRAs are recommended by our current national guideline as a less effective controller option in Step 2, as an add-on treatment to low-dose ICS-LABA in Step 3, as an add-on treatment to medium-dose ICS-LABA in Step 4, and as an add-on treatment to high-dose ICS-LABA, LAMA, or biological therapies in step 5 (2). GINA and our national guidelines provide more flexibility, allowing for LTRAs as an alternative in certain situations. In this study, we observed that montelukast was more preferred in Steps 4 and 5, similar to the UK. It may be speculated that the population's drug use characteristics and the impact of national guideline recommendations or warnings are likely to be associated with the variety of LTRA utilization rates.

LTRAs are beneficial in the long-term therapy of asthmatics who have allergic rhinitis, exercise-induced asthma, or aspirin-exacerbated respiratory disease.[24] Similarly, in our study, we found patients with allergic rhinitis, patients with hypersensitivity to nonsteroidal anti-inflammatory drugs, and chronic rhinosinusitis without nasal polyps used montelukast more often. A previous study found that patients with allergic rhinitis who began LTRA had a decreased probability of visiting the emergency department due to asthma.[25] Contrarily, in our study, we found no difference between allergic rhinitis patients who used montelukast and those who did not in terms of asthma exacerbation. However, patients with concomitant rhinitis had lower ACT scores. Furthermore, the high prevalence of allergic rhinitis in the montelukast group in our research implies that LTRA usage may be connected to this indication, but the fact that the majority of the patients were getting Steps 4 and 5 therapy suggests that they are used as an asthma controller medication. Allergic and eosinophilic asthma rates were found to be 65.4 and 57.2%, respectively in the registry.[17] In the study we conducted, it was determined that the IgE levels, blood eosinophil count and atopy rates supporting the allergic and eosinophilic asthma endotype (type 2 asthma) were higher in the montelukast group. These outcomes also demonstrate that, in light of the literature's knowledge, montelukast has established an appropriate patient profile. The excessive production of cysteinyl leukotrienes supports the possibility that NERD patients might benefit from the usage of LTRAs as a treatment.[26] In this regard, the montelukast study demonstrated favorable results for NERD patients, including improved asthma quality of life measures, reduced usage of rescue inhalers, and improved respiratory functions.[27] However, another study has not found any difference in the clinical response of montelukast-treated NERD patients.[28] NERD patients in the current study used montelukast at a high rate. However, because of the design of the study, it was not possible to assess changes in the patients' clinical and pulmonary function parameters after they began to utilize montelukast treatment.

In this registry, the majority of the participants in the subgroup who used montelukast were female. In addition to the high proportion of female patients using montelukast, the preponderance of these patients was on Steps 4 and 5. Asthma has a strong gender inequality.[29] Adult females have a higher prevalence (65%) than adult males.[30,31] Females have a greater lifetime risk of acquiring asthma and developing a more severe type of asthma than males.[32] This change in asthma incidence in males and females suggests genetic and epigenetic alterations, sex hormones, a complicated interaction of socioeconomic variables, and comorbidities.[33-35]

In addition, although the usage of montelukast was high in all age groups in our research, the use of montelukast was considerably greater in the 40–60 age group compared to the other two groups. Although the number of patients in the 40–60 age range was larger, it was assumed that adherence to therapy was similarly higher. According to previous studies, inhalant adherence in adult asthmatics is poorer than oral medicine compliance.[36,37] On the other hand, our study found that the use of montelukast was more prevalent

among those with a younger age of onset of asthma, while it was less prevalent among patients with an age of onset of asthma ≥ 65 years. According to a previous study, patients were more likely to be adherent to LTRA and more likely to be started on an LTRA rather than an ICS.[25] Besides, due to the high likelihood of misuse, particularly in certain groups like the elderly, ICSs are likely to fail to provide ideal therapeutic results.[38] A previous study revealed that the efficacy of ICS varies significantly depending on the level of health literacy of geriatric asthmatic patients, as the use of inhalers is complex and requires technical knowledge.[39] Given that unintentional nonadherence to inhalant therapy can impair asthma symptom control, it should be considered that leukotriene modifiers' simpler route of administration may improve asthma therapy outcomes in all age groups, especially in elderly patients.

Another important factor that must be taken into account is the patients' level of asthma control. While LTRAs demonstrated inferior effectiveness than ICS in clinical trials, in real-life studies, the incidence of asthma-related exacerbations in LTRA users was similar to that in ICS users.[25] In our study, variables indicative of asthma exacerbation were higher in the montelukast group. In addition, it was shown that patients in the montelukast group had lower ACT scores and uncontrolled asthma. In a previous study, montelukast positively impacted the quality of life in adult patients with mild to moderate persistent asthma but did not significantly improve ACT.[40] In the current study, it was observed that approximately 14% of partial or uncontrolled asthmatics did not utilize montelukast. It has been reported that the add-on therapy with anti-leukotrienes effectively decreases asthma exacerbations and improves lung function and asthma control in adolescents and adults with uncontrolled asthma with daily ICS.[41] Our study indicates that montelukast is often prescribed for severe and uncontrolled asthma patients, who nonetheless exhibit poorer asthma control outcomes. This finding likely reflects real-world prescribing practices where montelukast is added in complex, treatment-resistant cases where conventional therapies have limited effectiveness. Poorer control in this group may stem from the high disease burden and refractory nature of their asthma, rather than from the efficacy of montelukast itself. Anti-leukotrienes should be considered as an add-on medication in patients whose asthma control could not be achieved well with the current ICS dose and especially in patients whose inhaler treatment compliance is difficult, even though we cannot conclude from this study that their addition to the treatment is better to an increase in the ICS dose.

Despite the notable strengths of our study, which encompass a large sample size, standardized data entry procedures, and excellent representation of the patient population, there are also some limitations. First, the duration of patients' montelukast use was not specified, and their treatment adherence, discontinuation rates, and discontinuation reasons could not be questioned. In fact, it could not be evaluated whether the patients used all drugs or effective drugs. Second, patients' quality of life after initiation of montelukast treatment was not evaluated. Third, the effectiveness of montelukast therapy for patients was not assessed using an objective indicator. Finally, we have not received any reports of adverse events from patients with the use of montelukast. However, although this may be attributed to potential deficiencies in data entry or inadequate monitoring of side effects, it can also be interpreted as valuable real-world evidence regarding the safety profile of montelukast in adult patients, supported by data from 36 diverse centers.

In conclusion, for the first time, the utilization of montelukast in treating asthma patients was investigated using real-life data from our country, and it was observed that the vast majority of the patients received this medication. Our findings also indicated that montelukast is more frequently utilized in specific phenotypes and disease characteristics, particularly in advanced steps of asthma management. Considering higher uncontrolled asthma levels in patients receiving montelukast particularly, the reason behind this should be strategically analyzed and should be sought.

Authors Contribution

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation; has been involved in drafting the manuscript or revising it critically for important intellectual content.

Conflicts of Interest

The authors have no conflict of interest to declare.

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Statement of Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee (16-10l I-I7/2017) and written informed consent was collected from all study participants.

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Supplementary

Table S1 Treatment steps of patients based on asthma symptom control.

Variable	ACT < 20		ACT ≥ 20		P
	Not receiving montelukast	Receiving montelukast	Not receiving montelukast	Receiving montelukast	
Step 1	40 (15.4%)	8 (1.6%)	16 (5.2%)	14 (2.4%)	0.492
Step 2	27 (10.4%)	21 (4.2%)	39 (12.8%)	44 (7.6%)	0.124
Step 3	70 (27%)	101 (20.2%)	123 (40.2%)	155 (26.7%)	0.250
Step 4	63 (24.3%)	147 (29.4%)	50 (16.3%)	151 (26.1%)	0.336
Step 5	62 (23.9%)	223 (44.6%)	81 (26.5%)	216 (37.2%)	0.258

ACT, asthma control test.
Values are presented as number and percentage (%).