



## Physicians' preference for controller medication in mild persistent asthma



Arzu Bakirtas<sup>a,\*</sup>, Ali Kutlu<sup>b</sup>, Ayse Baccioğlu<sup>c</sup>, Ferda Oner Erkekol<sup>d</sup>, Sevim Bavbek<sup>e</sup>, Omer Kalayci<sup>f</sup>, Asthma Section Board Members of Turkish National Society of Allergy and Clinical Immunology<sup>g</sup>

<sup>a</sup> Department of Pediatric Allergy and Asthma, Gazi University School of Medicine, Ankara, Turkey

<sup>b</sup> Department of Emergency Medicine, Uskudar University, Istanbul, Turkey

<sup>c</sup> Department of Clinical Immunology and Allergic Diseases, Kirikkale University School of Medicine, Ankara, Turkey

<sup>d</sup> Department of Clinical Immunology and Allergic Diseases, Atatürk Training and Research Hospital, Ankara, Turkey

<sup>e</sup> Department of Clinical Immunology and Allergic Diseases, Ankara University Faculty of Medicine, Ankara, Turkey

<sup>f</sup> Department of Pediatric Allergy and Asthma, Hacettepe University School of Medicine, Ankara, Turkey

<sup>g</sup> Turkish National Society of Allergy and Clinical Immunology, Turkey

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### ABSTRACT

**Background:** Although the asthma guidelines recommend inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRAs) for the treatment of mild persistent asthma, factors governing the physicians' preference are unknown. We aimed to investigate the preference of physicians for the controller medication and the factors governing their choice.

**Methods:** A self-administered questionnaire composed of 16 questions that aimed to determine the preference of the physicians for the first choice controller medication in mild persistent asthma and physician and patient related factors that may be associated with this selection was e-mailed to the members of the Turkish National Society of Allergy and Clinical Immunology and distributed to participants in the 21st congress.

**Results:** Of the 670 questionnaires, there were 51% participants and 336 of them were complete enough to be included in the analysis. Low dose ICS was preferred as the first choice controller medication for mild persistent asthma by 84.5% of the physicians. The reasons for physicians' preference were different for ICS and LTRA. In the logistic regression analysis, use of asthma guidelines (OR:3.5, 95%CI:1.3–9.3,  $p = 0.01$ ), alignment in guidelines (OR:2.9, 95%CI:1.4–5.8,  $p = 0.002$ ) and the opinion that it is a more effective (OR:2.3, 95%CI:1.1–4.8,  $p = 0.02$ ) were independently associated with ICS preference. Being a pediatrician (OR:5.4, 95%CI: 2.7–10.5,  $p < 0.001$ ) and the opinion that it has better patient compliance (OR:4.4, 95%CI: 1.6–12.0,  $p = 0.004$ ) were independently associated with LTRA preference.

**Conclusion:** Surveyed Turkish physicians, the majority of whom were specialists, preferred ICS over LTRA as controller medication in mild persistent asthma. Asthma guidelines, training background (pediatrician versus not) and perceived efficacy and patient compliance appeared to influence their preferences.

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## 1. Introduction

Asthma is a chronic respiratory disease and almost half to three quarters of the patients have persistent symptoms [1]. According to Asthma Insights and Reality in Turkey (AIRET) Study, 72.7% of

children and 88.1% of adults with asthma were classified as having persistent disease in Turkey [2]. All asthma guidelines recommend a daily controller medication in persistent asthma in addition to a short acting inhaled bronchodilator as reliever [3–6]. Turkish physicians were guided by the most popular asthma guidelines as Global Initiative (GINA) and Turkish national ones [4,5].

National and global guidelines recommended either low dose inhaled corticosteroid (ICS) or leukotriene receptor antagonist (LTRA) as the initial treatment for mild persistent asthma [4,5].

\* Corresponding author. Gazi University School of Medicine, Department of Pediatric Allergy and Asthma, 06500 Besevler, Ankara, Turkey.

E-mail address: [arzubakirtas@gmail.com](mailto:arzubakirtas@gmail.com) (A. Bakirtas).

However, in the latest updates of these guidelines low dose ICS is the preferred one referring LTRA as less effective option which may lead to loss of asthma control [3–7]. Recommendations of regular controller medication in children  $\leq 5$  years are also not different as long as the symptoms are highly suggestive of asthma and preferred initial option is stated as regular daily low dose ICS plus as-needed reliever in the guidelines [4–6]. Regular LTRA had a modest effect on reducing asthma symptoms and need for oral corticosteroid course and Cochrane review concluded that LTRA had no superiority than placebo in young children with recurrent viral wheezing [4,7].

Even though these medications have been in the asthma armamentarium for many years, the search for the factors that predict a favorable response to either medication is largely unknown and it seems that a treatment trial is the most sensitive way to determine the response to each medication [9–11]. There are some clues associated with a favorable response to ICS (high levels of exhaled nitric oxide, total eosinophil counts, levels of serum IgE, and levels of serum eosinophil cationic protein and lower levels of methacholine PC(20) and pulmonary function, parental history of asthma and previous history of ICS use) [8–14] and to LTRA (younger age and shorter disease duration) [9,11] that may aid the physicians in determining their first choice medications in the treatment of mild persistent asthma. The use of LTRA may have also a more specific target population with concomitant allergic rhinitis, exercised induced or aspirin exacerbated asthma [15–18].

There are also patient related factors in the choice of controller medications such as lower velocity growth under ICS, poor inhaler technique, unwilling to use ICS, and experienced intolerable side effects of ICS that might also be considered by the specialized physicians' practise [4–6].

Some non-evidence based factors which are not mentioned in the guidelines might also influence highly specialized physician in their decision on starting controller medicine such as obesity, diabetes or hypertension as being a contraindication to ICS treatment, or avoiding LTRA in patients with psychological problems.

We hypothesized that physicians prefer inhaled corticosteroid as first line treatment since current guidelines indicate it as the most appropriate regimen for patients with mild persistent asthma. We also wanted to investigate whether there are some other physicians and patient related factors that are not written in the guidelines which may influence physicians' first choice of controller medications as a secondary aim.

## 2. Methods

An 18 question questionnaire was designed by the authors to investigate physician's preference in asthma prescribing (Appendix). The questionnaire was not validated and pre-testing was not done. The core question was about the preference of the physicians for the first choice controller in mild persistent asthma. Physicians could choose only one controller medication: ICS or LTRA. Thirteen questions were about the possible physician related factors that could be related with this choice. We also included questions on the physicians' opinion regarding predictors of good response, patient related factors for preference of physicians and the choice of add-on treatment for asthmatic patients  $\leq 5$  years and  $> 5$  years old in the step up approach.

The study's target population was the physicians dealing with asthma patients. In Turkey, family physicians, pediatricians, internal medicine physicians, pulmonologists and allergists can see, diagnose and manage asthma patients. They all can prescribe ICS, LTRA but only allergists and pulmonologists can prescribe combination (ICS plus LABA), LABA and anti-IgE. It is also recommended that patients who need step 3 of national or GINA asthma guideline

be referred to either an allergist or pulmonologist. Allergy congress is a good sample of the above profile. Therefore, we delivered the questionnaires to physicians when they apply for registration at the congress registration desk throughout the congress 21st National Allergy and Clinical Immunology Congress held in November 2014. The questionnaire was also e-mailed to the members of the Turkish National Society of Allergy and Clinical Immunology. The participation was purely on a voluntary basis and by completing the survey it was implied that consent was given to participate in the study. The study population was composed of physicians who returned the completed forms. The study was approved by the Ethics Committee of Gazi University School of Medicine (Protocol 13 Oct 2014/#459).

## 3. Data analysis

Data from completed questionnaires were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp USA). Chi-square test was used to test for significant differences between the categorical variables. Continuous variables were compared using Student's *t*-test or Mann-Whitney *U* test depending on the normality of distribution. Multivariate logistic regression analysis was used to determine the factors associated with preference of physicians for the first controller medication. A *p* value of less than 0.05 was considered to be significant.

## 4. Results

There were 342 physicians who responded among 670 questionnaires that were delivered (51.0%). Six questionnaires were not included in the analysis because the question regarding the choice of controller medication was not answered (Table 1). Ninety four percent of physicians were specialists and 47.9% of the physicians were adult pulmonologists. Forty eight percent of the physicians were employed at a university hospital and 69.3% of physicians were following only adult asthma patients. Median number of asthma patients seen by the physicians was 40 per month (Table 1).

**Table 1**  
Demographic characteristics of participants (Questionnaire part-I).

	n:336
Q1. Age, yr (25p-75p)	38.5 (32.7–42.2)
Q2. Male, n (%)	181 (53.9)
Q3. Specialist, n (%)	319 (94.9)
Q4. Spectrum of physicians, n (%)	
Adult pulmonologist	161 (47.9)
Pediatrician	67 (19.9)
(non-allergist/ non-pulmonologist)	
Internal medicine	35 (10.4)
(non-allergist/non- pulmonologist)	
Pediatric allergist	29 (8.6)
Adult allergist	20 (6.0)
Family physician	15 (4.5)
Pediatric pulmonologist	6 (1.8)
Chest surgery	1 (0.3)
Missing	2 (0.6)
Q5. Affiliation, n (%)	
University hospital	165 (48.2)
State training and research hospital	96 (28.1)
State hospital	47 (13.7)
Private hospital	29 (8.5)
Private office	5 (1.5)
Q6. Graduation year, yr (25p-75p)	1999 (1992–2006)
Q7. Asthma outpatient visit/month, n (25p-75p)	40 (10–150)
Q8. Age spectrum of patients followed by the physicians', n (%)	
Adult	233 (69.3)
Children	99 (29.5)

Continuous parameters were shown as median (25p-75p).

Low dose ICS was the preferred medication for mild persistent asthma by 84.5% of the physicians (see Table 2). One third of the physicians recommend intermittent use of controller treatment among whom the choice of ICS (88/113: 77.9%) was more frequent than LTRA (25/113: 22.1%) (p:0.001).

The major factors that guided the physicians in their choice of first line treatment were good patient compliance (74.1%), higher effectiveness (72.6%) and ease of use (72.3%). These factors for preference were significantly different with respect to the preferred medication (Table 3). The most frequent reasons for non-preference were poor patient compliance (49.4%), being recommended as the

alternative choice in the guidelines (45.2%), lower effectiveness (45.2%) and difficulty to use (41.1%).

The main reasons for preference of LTRA over ICS were better patient compliance and ease of use; and those for preference of ICS over LTRA were higher effectiveness and having a priority in the guidelines.

The two groups, those who preferred ICS and those who preferred LTRA were compared with respect to many variables as listed in Table 4. Factors that showed a significant association in the univariate analysis were included in the multivariate logistic regression to determine the variables that showed an independent association (Table 5). The use of asthma guidelines, recommendation as the preferred controller treatment in the guidelines and higher effectiveness were associated with ICS preference whereas being a pediatrician and better patient compliance were associated with LTRA preference (Table 5).

**Table 2**

Questionnaire part-II (n: 336).

	n (%)
Q9. Use of asthma guidelines	
Yes	300 (89.3)
No	32 (9.5)
Q10. Attend an asthma course/congress	
Yes	259 (77.1)
No	74 (22.0)
Q11. Last time to attend an asthma course/congress	
≤5 years ago	261 (77.7)
>5 years ago	23 (6.8)
Q12. Which parameters do you use to decide on the type of controller treatment for asthma? (Can select more than one)	
Symptoms/Physical examination findings	314 (93.5)
Asthma control test	133 (39.6)
Pulmonary function test	235 (69.9)
Exhaled nitric oxide	6 (1.8)
Q13. How do you recommend the use of controller treatment?	
Continuously	218 (64.9)
Intermittently	113 (33.6)
Q14. Controller treatment preference for mild persistent asthma (GINA Step 2)	
ICS	284 (84.5)
LTRA	52 (15.5)

ICS: Inhaled corticosteroids; LTRA: Leukotriene receptor antagonists; LABA: Long-acting  $\beta_2$ agonist.

## 5. Discussion

Low dose ICS and LTRA are the two main choices for pharmacotherapy in mild persistent asthma [3–6]. Even though there are some data concerning the predictors of the treatment response to each medication [7,9,11], the main factors that underlie the clinicians' choice of the initial treatment are unknown. We aimed to investigate the factors governing the physicians' choice in the treatment of mild persistent asthma. We found that ICS was preferred as the first choice by 85% of the physicians surveyed in this study.

All asthma guidelines recommend ICS as the preferred controller medication not only at the initial step but also at the step-up treatment both in adults and in children with persistent disease [3–7]. Therefore, it is not surprising that most of the physicians included in the study preferred ICS as the first line controller medication for mild persistent asthma. This result is a good point that most of the physicians seem to make guideline driven choices.

On the other hand, the results indicate that some of the

**Table 3**

Major factors that guided the physicians in their choice of first line treatment (Questions 15 and 16) (Can select more than one).

	Physicians who prefer		p
	ICS (n:284)	LTRA (n:52)	
<b>PHYSICIAN RELATED FACTORS</b>			
Ease of use, n (%)	198 (70.0)	45 (86.5)*	0.014
Better patient compliance, n (%)	202 (71.4)	47 (90.4)*	0.004
More effective, n (%)	213 (75.3)*	31 (59.6)	0.020
Fewer side effects, n (%)	136 (48.1)	27 (51.9)	0.608
Preferred controller choice in the guidelines, n (%)	166 (58.7)*	21 (40.4)	0.015
Physician has more experience with it, n (%)	71 (25.1)	13 (25.0)	0.989
Cheaper, n (%)	61 (21.6)	9 (17.3)	0.489
<b>PATIENT RELATED FACTORS</b>			
Presence of aeroallergen sensitization, n (%)	78 (27.6)	12 (23.1)	0.721
Comorbid allergic rhinitis, n (%)	84 (29.7)	19 (36.5)	0.325
Symptoms triggered only with URTI, n (%)	42 (14.8)	4 (7.7)	0.169
Triggers other than URTI, n (%)	57 (20.19)	8 (15.4)	0.425
Hospitalization due to asthma, n (%)	125 (44.29)	19 (36.5)	0.307
Frequent ED visits due to asthma, n (%)	155 (55.0)	21 (40.4)	0.053
Exercise-dependent symptoms, n (%)	74 (26.1)	14 (26.9)	0.907
NSAID-dependent symptoms, n (%)	41 (14.5)	5 (9.6)	0.344
Age of the patient, n (%)	57 (20.1)	12 (23.1)	0.630
Presence of obesity, n (%)	32 (11.3)	1 (1.9)	0.067
Comorbid DM, HT, n (%)	46 (16.3)	4 (7.8)	0.121
Preference of the patient, n (%)	58 (20.5)	12 (23.1)	0.674
Other reasons, n (%)	2 (0.7)	0 (0)	0.542

\*p < 0.05 compared to the other controller medication; DM: Diabetes Mellitus.

HT: Hypertension, URTI: Upper respiratory tract infection, ED: Emergency department.

**Table 4**

Univariate analysis of factors that guide physicians' choice for the controller medication in mild persistent asthma.

	Physicians who prefer				
	ICS (%)	LTRA (%)	OR	95%CI	p
Male	51.4	71.2	0.42	0.2–0.8	0.009
Pediatrician	24.5	63.5	0.18	0.1–0.3	<0.001
Adult pulmonologist	55.3	21.2	4.61	2.2–9.3	<0.001
Age spectrum of the patients (Adult patients)	76.5	35.3	5.97	3.1–11.2	<0.001
Use of asthma guidelines	92.1	80.8	2.79	1.2–6.3	0.01
Has ever attended an asthma course or congress?	80.8	61.5	2.62	1.3–4.3	0.002
Continuous use of controller medication	77.2	22.8	2.15	1.2–3.5	0.003
More effective treatment	75.3	59.6	1.81	1.1–2.9	0.02
Recommended as preferred in guidelines	58.7	40.4	1.86	1.1–3.1	0.015
Ease of use	70.0	86.5	0.80	0.7–0.9	0.02
Better patient compliance	71.4	90.0	0.79	0.7–0.8	0.007

**Table 5**

Multivariate analysis of factors that guide physicians' preference for ICS or LTRA.

	LTRA		
	OR	95% CI	p
Male	0.5	0.2–1.01	0.054
Pediatrician	5.4	2.7–10.5	<0.001
Ease of use	1.8	0.7–4.9	0.204
Better patient compliance	4.4	1.6–12.0	0.004
	ICS		
	OR	95% CI	p
Adult pulmonologist	1.5	0.5–4.3	0.41
Age spectrum of the patients (Adult patients)	2.7	0.7–9.4	0.11
Use of asthma guidelines	3.5	1.3–9.3	0.01
Has ever attended an asthma course or congress?	1.2	0.5–2.9	0.53
Continuous use of controller medication	1.5	0.7–3.2	0.20
More effective treatment	2.3	1.1–4.8	0.02
Recommended as preferred in guidelines	2.9	1.4–5.8	0.002

physicians may prefer intermittent use of controller medications which is not recommended either for or against in the guidelines [3–7]. Even though the underlying rationale behind this preference was not questioned in the questionnaire, the low level of patient compliance observed by the physicians may be a factor.

In clinical trials with adults and children, high bronchodilator response and low pulmonary functions [8,9,13], high levels of allergic inflammation [8,9,11], aeroallergen sensitization [10,12] and high disease burden such as oral corticosteroid use, ED visit or hospitalization in the previous year [10,12] were shown to be predictors of good ICS response. On the other hand, younger age and shorter disease duration in children [9], smoking [16] or comorbidity of asthma and allergic rhinitis [17,18] may be associated with a favorable response to LTRA. In this respect, it is interesting to note that none of the parameters investigated in the pointed studies had any effect in the physicians' choice in this study. This may be because the guidelines do not recommend routinely the measurement of these biomarkers before the prescription of controller medication [4,5]. In addition, most of these investigations such as allergen sensitization by skin prick tests or specific IgE measurements, exhaled NO, bronchial hyperreactivity are not readily available in most of the daily practise and therefore these factors may be favored in the academic world but seem not to have influenced general asthma physicians' choice. Therefore, we concluded that the influence of these biomarkers in physicians' controller choice may be more suitable to study in another study with a very specialized population of physicians such as pulmonologists and allergist: do they use them in mild persistent asthma as in severe asthma; when do they use them: at initiation of

treatment or when the patient with mild persistent asthma did not response to initial treatment; which biomarkers do they prefer and is it cost effective in mild persistent asthma? Although we hypothesized that physicians may also be basing medication choices on non-evidence based patient related factors such as obesity or psychological issues, the survey results did not support it, either.

This study showed that different specialties seem to favor different controller therapy such as LTRA preference by pediatricians which might be due to the different educational backgrounds of the specialties.

Interestingly, the cost of the medication had no effect in the choice of the controller medication. This is most likely due to the fact that all asthma medications are reimbursed by the Ministry of Health in our country, and most people are under insurance coverage even refugees in Turkey. However, this finding should be considered by the health planning authorities in national campaigns.

In contrast to the suggestions in the guidelines [3–7], the physicians treating asthma patients in this study did not seem to consider patient preference in their choice of the medication. Since this may result in decreased patient compliance, it may be an indication to consider patient preference in educational activities. Taken together, our data suggest that the decision of the physicians seem to be influenced by physician related factors rather than patient-related factors or clinical, functional and inflammatory predictors of good treatment response. However, it should be acknowledged that this finding may be due to the fact that the questions were related to mild persistent asthma only and did not cover severe asthma where biomarkers that predict a treatment response are better studied.

This study has some limitations. First of all, the questionnaire that we used has not been validated for this purpose. Secondly, the study population comprised of physicians dealing with asthma on a specialist basis and therefore the results may not reflect the attitude of the general approach by the general practitioners in the country. For example, the safety profile which had no effect on the physicians' choice in this study may be expected to have a role in the general practitioner's or pediatricians' choice. Thirdly, the questionnaire-based nature of the study may be another limitation because the data are based on self-reporting and we do not have an objective measure of actually prescribed medicine. Finally, the questionnaires were distributed at the registration desk and they were completed at some point during the congress. It is possible that this timing might have affected the outcome. For example, if they were filled immediately after hearing a talk on the guidelines, the participant may have chosen responses that may comply more with the written guidelines. Even if this is not the case, the fact that the questionnaires were actually filled either during or

immediately after a congress that update the physicians may have had an effect as well.

In conclusion, our study provides the initial data about the factors that govern physicians' attitudes in prescribing the first line treatment in mild persistent asthma and may help planning future studies to investigate the reasons behind these choices with better methods, educational activities and health care policies.

#### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2017.08.029>.

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