



Adherence, quality of life, and satisfaction with conventional fixed combined therapy versus maintenance and reliever therapy in patients with asthma after inhaler training

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ABSTRACT

Objective: Treatment adherence, asthma control, inhaler satisfaction, and quality of life of patients with asthma were investigated to examine whether there were any differences between conventional fixed combined therapy and maintenance and reliever therapy after inhaler education.

Methods: Cross-sectional observational follow-up of 120 patients with asthma receiving third- and fourth-step treatment was completed at zero, three, and six months. Fifty-eight patients received long-acting beta-agonists or inhaler corticosteroids (ICS) as maintenance therapy and short-acting beta-agonists (SABA) as reliever therapy (CONV) with Diskus and Ellipta devices. Sixty-two patients received ICS/formoterol as maintenance and reliever therapy (MART) with metered-dose inhaler and Turbuhaler devices. The asthma control test (ACT), feeling of satisfaction with the inhaler (FSI-10) questionnaire, Morisky Green Levine (MGL) scale, and quality of life questionnaire (AQLQ) were evaluated at each visit.

Results: Significant improvement was observed in the ACT, AQLQ, FSI-10, MGL scales, and inhaler technique in both groups over time ($p < 0.05$). There was no difference in the MGL scale between the groups at all visits. Nonadherence was highest in the Diskus device group (55%) and lowest in the Ellipta device group at the first visit (25%). While 36% of the patients had low adherence at the first visit, this decreased to 12% by the last visit. A significant correlation was found between ACT and MGL at all visits ($p < 0.001$).

Conclusion: Asthma control, adherence, inhaler satisfaction, and quality of life improved equally with regular follow-up and standard inhaler education in the CONV and MART groups.

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Introduction

In addition to pharmacological treatment, physician-patient collaboration, patient education, satisfaction, and adherence are important for improving asthma control and patient's quality of life (1).

Stepwise treatment aims to adjust the treatment based on asthma control and apply the ideal treatment (1). There are two approaches suggested as treatment options in third, fourth, and fifth step cases: 1) combination of maintenance inhaler corticosteroids (ICS)/long-acting beta-agonists (LABA) with short-acting beta-agonist (SABA) reliever therapy (CONV), 2) combination of ICS/formoterol as maintenance and reliever therapy (MART) (1).

Few studies have compared these two therapeutic methods in terms of adherence to treatment and

quality of life after standard education on using inhalers is provided (2–4). No studies were found that evaluated the use of different inhalers and treatment protocols in actual clinical practice (5,6).

The current study was designed as there was no research questioning the adherence in which the two treatment protocols (MART and CONV) and the devices suitable for them were used together, by searching the literature. There is no study in the literature comparing two devices from the MART group, two devices from the CONV group, and these two main groups together. The present study was conducted on patients with asthma on CONV or MART therapy as third or fourth-step treatment. We provided standard education to both groups and aimed to determine whether there were any differences in

asthma control, adherence to therapy, and quality of life between the groups. Secondly, we aimed to show whether there were any differences in the investigated parameters due to the education on asthma and inhaler use, despite different inhalers being used. Comparisons between groups were made before and after inhaler training.

Materials and methods

Study design and setting

This prospective, observational, real-life cohort study was conducted between January 2018 and June 2019 on patients that presented to the outpatient clinic of our department and met our inclusion and exclusion criteria. The Institutional Ethics Committee of our institution approved the current study (83045809–604.01.02) in December 2017.

Patients

The inclusion criteria were

- Patients with controlled or uncontrolled asthma aged 18 to 65 years who were diagnosed with asthma based on the Global Initiative for Asthma criteria (1), were attending the outpatient clinic for regular follow-ups, and receiving third or fourth-step treatment (both "Adult Onset" and patients with "Childhood Asthma");
- Patients that agreed to participate in the study after giving their written informed consent;
- If they had comorbidities such as rhinitis or gastroesophageal reflux, these had to be controlled spontaneously or with treatment.

The exclusion criteria were:

- Patients at the first, second, or fifth step of treatment,
- Patients that experienced severe exacerbations requiring systemic steroids at baseline,
- Presence of uncontrolled comorbidities,
- Presence of any condition that required an inhaler (chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, etc.),
- Pregnancy.

Variables

At the first visit, a hard copy and web-based registration form for Asthmatic Patients of the Turkish

Thoracic Society was completed by the participants. The following was recorded on this form: demographic characteristics, diseases, exposures they had during childhood, comorbidities, family history, symptoms, symptom control status, disease triggers, laboratory values, medications, the number of exacerbations, inhalers technique, and therapeutic adherence. The Inspection Form for the Asthmatic Patients of the Turkish Thoracic Society was completed.

Measurements

Asthma control test (ACT)

The ACT is a questionnaire that consists of five domains that query patient's day- and nighttime manifestations of asthma, use of rescue drugs, and limitations in daily living activities due to asthma. The validated Turkish version was used. For ACT scoring, points between 20 and 25 were considered as "controlled" and those below 20 as "uncontrolled" (7,8). The three points in the ACT is significant for measuring improvement following treatment (7,8).

Morisky Green Levine (MGL) medication adherence scale

After permission was sought from the authors, the MGL Medication Adherence Scale was used. This contains four items that are marked as "Yes/No." The MGL scale gives points ranging from 0 to 4: a score of 0 indicates good or satisfactory adherence, 1–2 points partial adherence, and 3–4 points nonadherence (9,10). The MGL scale contains four out of eight items of the MMAS-8 Medication Adherence questionnaire, of which the Turkish version was validated (11).

Feeling of satisfaction with the inhaler (FSI)-10 questionnaire

The FSI-10 was used to quantify patient's satisfaction with the inhalers they used for maintenance treatment. The FSI-10 questionnaire contains ten items with five possible responses on the Likert Scale (very easy, quite easy, almost easy, not so easy, and not easy at all), and responses are scored from five to one. The maximum score was 50 and the minimum score ten. Higher scores indicate a higher level of satisfaction. This questionnaire included items related to patients' satisfaction level with the inhalers they were using, ease of handling, portability, and usability (12,13).

Asthma quality of life questionnaire (AQLQ)

To evaluate quality of life, the Turkish version of the AQLQ was used. This question consists of 32 items

under four main headings. The main headings were asthma symptoms (12 items), activity restriction (11 items), environmental factors (four items), and emotional function (five items). The questionnaire evaluates the patients' experience over the last two weeks using a seven-point scale (1: severe deterioration, 7: No deterioration). The total score and mean scores for each heading were calculated. A change in the score of more than 0.5 is considered clinically significant (14–16)

Pulmonary function tests

Spirometric tests were performed with a spirometry device (ZAN 100 Flow Handy II, Germany). The tests were performed in accordance with the ERS/ATS criteria (17). The best FVC, FEV₁, and FEV₁/FVC values were recorded.

Exacerbations

At the first visit, the patients were asked about the number of exacerbations in the last 1 year. In the 2nd and 3rd visits, they were asked how many exacerbations they have had since the last visit.

Study size

Epi Info software was used to determine the power of the study. It was determined that each group should contain at least 42 patients based on a risk ratio of 5% with an 80% confidence interval as a different group cohort sectional study and at least 58 patients per group to determine the difference in adherence.

Quantitative variables

Follow-up of the patients was carried out using the First Registration Form and Inspection Form of the Turkish Thoracic Society. The ACT, MGL, AQLQ, and FSI-10 satisfaction questionnaires were used, and spirometry was performed at the baseline and follow-up visits at zero, three, and six months ($\pm$ 5 days). At each visit, patients' use of the inhalers was evaluated, and they were given inhaler training. A team of 3 physicians was determined for inhaler technical training and evaluation. Inhaler technical evaluation was made by 2 physicians. Inhaler training was given by the third physician at each visit. The person giving the training and the people evaluating the training were planned separately. Inhaler technique training was provided both by watching videos and by explaining face to face. They watched training videos from

the Turkish Thoracic Society (<https://www.youtube.com/watch?v=yeXOxbQqG54>) website and were explained how to access the site if required. No treatment changes were made during the follow-up period. All patients had an asthma management plan similar to that recommended by GINA. Since the GINA guideline suggested that the inhaler technique should be checked and retrained at each visit, the patients were trained at each visit, regardless of the inhaler technique. The patient who had an exacerbation was treated by giving oral steroids (3–7 days) during the exacerbation period

The patients' data were entered into the asthma database and transferred from this database to Microsoft Excel for analysis.

The patients were divided into two groups based on the medications they were using. No changes were made in the treatments and devices used by the patients. The devices used by the patients who were accepted to participate in the study during the determined period were evaluated. The CONV group included patients using the Diskus and Ellipta devices, whereas the MART group included patients using Turbuhaler and metered-dose inhalers (MDIs). Differences between the groups and changes between the follow-up visits were compared in terms of asthma control, satisfaction with the inhaler, medication adherence, and quality of life.

Statistical analyses

Data from 120 patients were recorded, including 58 and 62 from the CONV and MART groups, respectively. Numeric data were presented as the average, standard deviation, median, minimum, and maximum values, whereas the categorical variables were presented as numbers and percentages. In two-group comparisons for the numeric parameters, the Mann-Whitney U test was used for numeric parameters with an uneven distribution. Wilcoxon's test was used to compare the values measured at the three time points. The Friedman test was done and it was significant. In order to understand the difference between which two times, a binary time comparison was made. Group comparisons of the categorical variables were performed using cross-table statistics (Chi-square tests, Pearson's chi-square test, Mantel-Haenzel, Fisher's exact test). Categorical variables measured at the three time points were analyzed using McNemar-Bowker's test. A logistic regression model was used to determine the factors that affect the adherent/non-adherent parameters of the MGL variable. A p values of < 0.05 was considered

statistically significant. The significance level of p values with Bonferroni correction was calculated according to the number of comparisons. Since we compared 3 visits, the p values was calculated as approximately $0.05/3 = 0.017$.

Results

Patients

A total of 138 patients agreed to participate in the study and provided their written informed consent. However, only 120 patients were included in the final analysis because five and 13 patients did not present for the second and third visits, respectively. The MART and CONV groups included 62 (52%) and 58 (48%) patients, respectively.

Socio-demographic characteristics, comorbidities, and allergic diseases

The socio-demographic characteristics, comorbidities and allergic diseases of the patients included in the current study are summarized in Table 1. Diagnoses of allergic rhinitis and GERD were made based on the medically confirmed history of patients.

Distribution of the patients in the groups based on therapeutic steps and used inhalers

As shown in Table 2, the number of those on third- and fourth-step treatment were similar in both groups. However, findings on two different devices were obtained because of the different medications used in the groups.

Inhaler technique

There was no significant difference between the groups at visit one, while a remarkable increase was seen in those on CONV group at visits two and three ($p < 0.001$; Table 3).

Pulmonary function test results

The pulmonary function test parameters at visits one, two, and three are shown in Table 4. No significant difference was found in these parameters between the MART and CONV groups.

ACT results

No significant difference was found in the ACT results between the MART and CONV groups (Figure 1). A

significant difference was found in the direction of increase in ACT results at the following visits when the differences between visits were examined ($p < 0.001$; Figure 1).

For the patients using the Diskus and Ellipta devices, significant differences were found parallel to the improvement in ACT results when differences between visits one and two, visits two and three, and visits one and three were examined (Table 5). No significant difference was found in the ACT between patients using different devices ($p > 0.05$).

MGL scale results

No significant difference was found in medication adherence at all three visits between both groups when medication adherence was evaluated using the MGL scale (Table 6).

In both the MART and CONV groups, significant differences were found in the MGL scale results when visits one and two ($p = 0.01$ for the MART group and $p = 0.03$ for the CONV group), one and three ($p < 0.001$ for the MART group and $p < 0.001$ for the CONV group), and two and three were compared ($p = 0.026$ for the MART group and $p = 0.117$ for the CONV group).

MGL scores at 95% confidence interval are shown in Table 7. In the comparison between the two groups using the MWU test while there was no statistically significant difference between the two groups, there was a significant increase in treatment adherence from the first visit to the last visit (Table 5).

The devices were evaluated for adherence at each visit. When the first visit results were evaluated, the rate of nonadherence was found to be twice as high for the Diskus and MDI devices than for the Ellipta and Turbuhaler devices. Ellipta had a higher rate of adherence than the other devices ($p = 0.037$; Table 6).

A logistic regression analysis was used to evaluate patients' adherence according to their age, educational level, body mass index, smoking status, asthma control, quality of life, satisfaction with their inhaler, and treatment group. No significant relationship was found between these parameters and medication adherence.

FSI-10 questionnaire results

No significant difference was found in the FSI-10 questionnaire results when both groups were compared at visits one and two. However, a significant difference was found between the groups at visit three in favor of the CONV group (Table 5). The FSI-10 questionnaire results are summarized in Table 4.

Table 1. Socio-demographic characteristics and comorbidities and allergic diseases.

	MART N=62	Conventional N=58	p
Gender; n (%)			0.659
Female	44(71)	39(67)	
Male	18(29)	19 (33)	
Age (mean ± SD)	45.3 ± 15.3	48.1 ± 15.9	0.419
Age at the time of diagnosis (mean ± SD)	35.2 ± 14.1	37.4 ± 15.0	0.359
BMI (mean ± SD)	28.4 ± 6.1	27.6 ± 4.6	0.797
Educational level; n (%)			
Primary school	17 (28)	27 (47)	
High school	14 (23)	9 (16)	
University/College	27 (44)	20 (35)	
Smoking status; n (%)			
Never smoked	42 (68)	34 (58)	
Smoked, quit	15 (24)	12 (21)	
Current smoker	5 (8)	12 (21)	
History of having Pet; n (%)			
Age ≤ 16, pet in the house	5 (8)	17(29)	0.003
Age > 16 pet in the house	7 (11)	11 (19)	0.239
Current presence of pet in house	3 (5)	8 (14)	0.089
Exposure to cattle/small cattle during early childhood (<6 years)	13 (21)	18 (31)	0.208
Allergic rhinitis; n (%)	43 (69)	43 (74)	0.561
Sensitivity to analgesics; n (%)	1 (2)	5 (9)	0.078
Bee allergy; n (%)	0 (0)	1 (2)	
Food allergy; n (%)	1 (2)	3 (5)	
Atopic dermatitis; n (%)	4 (7)	4 (7)	0.922
Urticaria; n (%)	2 (3)	0 (0)	
Thyroid diseases; n (%)	6 (10)	7 (12)	0.674
Cardiac conditions; n (%)	8 (12)	7(12)	0.890
Hypertension; n (%)	7 (11)	6 (10)	
Cardiac failure; n (%)	1 (2)	1 (2)	
Coronary arterial disease; n (%)	2 (3)	4 (7)	0.428
GERD; n (%)	14 (23)	15 (26)	0.675
Diabetes; n (%)	7(11)	7 (12)	0.894
OSAS; n (%)	0 (0)	2(3)	0.232

Table 2. The used inhaler devices and treatment steps.

	MART N=62	CONV N=58	Total N=120
Treatment step; n (%)			
Third step	47 (78)	40 (68)	87 (72)
Fourth step	15 (22)	18 (31)	33 (28)
Used devices; n (%)			
Diskus	0	22 (38)	22 (18)
Ellipta	0	36 (62)	36 (30)
MDI	28(45)	0	28 (23)
Turbuhaler	34 (55)	0	34 (28)

MDI and Turbuhaler devices were used in the MART group and Diskus and Ellipta devices were used in the CONV group. In the MART group, 78% of the patients received third-line therapy, in the CONV group, 67% of the patients received third-line therapy.

Table 3. Techniques of using inhalers at the visits.

	Visit 1			Visit 2			Visit 3		
	CONV; (n%)	MART; (n%)	Total; (n%)	CONV; (n%)	MART; (n%)	Total; (n%)	CONV; (n%)	MART; (n%)	Total; (n%)
Inappropriate; (n%)	14 (24)	13 (33)	27 (28)	1 (2)	20 (39)	21 (19)	0 (0)	18 (34)	18 (16)
Partially appropriate; (n%)	11 (19)	3 (8)	14 (14)	5 (9)	0 (0)	5 (5)	1 (2)	0 (0)	1 (1)
Appropriate; (n%)	33 (57)	24 (60)	57 (58)	51 (90)	32 (62)	83 (76)	57 (98)	34 (65)	91 (83)
Total; (n%)	58 (100)	62(100)	120(100)	58 (100)	62(100)	120(100)	58 (100)	62(100)	120(100)

The *p* values of the change in inhaler technique between Visit 1 and Visit 2 was determined as *p*=0.244, and the *p* values of the change in inhaler technique between Visit 2 and Visit 3 was determined as *p*<0.001.

AQLQ results

In the symptoms and activity restriction sections, no significant differences were found in the AQLQ results

between the groups (Table 3). Statistically significant differences parallel to each visit's improvement were found when the MART and CONV groups were compared between visits (Table 6).

Table 4. Pulmonary function tests, FSI-10 questionnaire, AQLQ questionnaire at each visit.

		N	Visit 1		Visit 2		Visit 3	
			Mean $\pm$ SD	<i>p</i>	Mean $\pm$ SD	<i>p</i>	Mean $\pm$ SD	<i>p</i>
FEV 1	CONV	58	2.31 $\pm$ 0.94	0.629	2.46 $\pm$ 0.96	0.903	2.43 $\pm$ 0.92	0.941
(lt)	MART	62	2.58 $\pm$ 2.12		2.48 $\pm$ 0.88		2.46 $\pm$ 0.90	
% FEV 1	CONV	58	78.33 $\pm$ 16.28	0.279	84.78 $\pm$ 15.48	0.187	84.16 $\pm$ 15.90	0.477
	MART	62	75.69 $\pm$ 14.54		82.34 $\pm$ 14.78		82.07 $\pm$ 15.62	
FVC	CONV	58	3.35 $\pm$ 1.27	0.909	3.50 $\pm$ 1.29	0.805	3.49 $\pm$ 1.24	0.715
(lt)	MART	62	3.33 $\pm$ 1.13		3.46 $\pm$ 1.17		3.46 $\pm$ 1.19	
% FVC	CONV	58	96.16 $\pm$ 15.06	0.047	100.86 $\pm$ 13.31	0.007	100.88 $\pm$ 16.24	0.028
	MART	62	88.08 $\pm$ 24.26		87.37 $\pm$ 31.33		87.89 $\pm$ 31.67	
FEV1/FVC	CONV	58	67.83 $\pm$ 9.12	0.742	70.17 $\pm$ 8.37	0.918	69.57 $\pm$ 10.21	0.760
(%)	MART	62	65.47 $\pm$ 16.77		64.68 $\pm$ 22.85		63.95 $\pm$ 23.12	
FEF 25–75	CONV	58	1.62 $\pm$ 1.08	0.277	1.67 $\pm$ 0.96	0.699	1.73 $\pm$ 0.99	0.530
(lt/sec)	MART	62	1.35 $\pm$ 0.81		1.62 $\pm$ 1.21		1.57 $\pm$ 0.98	
% FEF 25–75	CONV	58	40.90 $\pm$ 20.18	0.613	45.19 $\pm$ 20.16	0.525	45.14 $\pm$ 20.77	0.348
	MART	57	41.63 $\pm$ 17.98		49.16 $\pm$ 25.21		47.82 $\pm$ 20.09	
PEF	CONV	58	5.54 $\pm$ 2.00	0.880	6.12 $\pm$ 2.26	0.899	6.08 $\pm$ 1.93	0.600
(lt/sec)	MART	57	5.56 $\pm$ 1.86		6.15 $\pm$ 2.26		5.99 $\pm$ 2.05	
% PEF	CONV	58	78.74 $\pm$ 22.13	0.814	87.72 $\pm$ 27.86	0.636	85.97 $\pm$ 21.89	0.669
	MART	57	76.91 $\pm$ 18.06		84.96 $\pm$ 18.49		85.21 $\pm$ 16.95	
FSI-10	CONV	58	44.4 $\pm$ 7.5	0.510	47.2 $\pm$ 3.9	0.777	48.7 $\pm$ 2.7	0.037
	MART	62	44.3 $\pm$ 6.3		46.6 $\pm$ 5.1		47.1 $\pm$ 4.4	
AQLQ Symptoms	CONV	58	55.3 $\pm$ 15.1	0.920	63.2 $\pm$ 13.1	0.412	69.3 $\pm$ 11.2	0.889
	MART	62	55.1 $\pm$ 16.1		65.3 $\pm$ 12.6		70.3 $\pm$ 14.2	
AQLQ Activity Restriction	CONV	58	45.3 $\pm$ 16.2	0.916	53.6 $\pm$ 12.5	0.567	57.3 $\pm$ 13.1	0.690
	MART	62	45.5 $\pm$ 14.5		52.0 $\pm$ 12.9		56.4 $\pm$ 13.0	
AQLQ Emotional Function	CONV	58	21 $\pm$ 7.9	0.597	24.5 $\pm$ 7.2	0.597	24.8 $\pm$ 6.6	0.719
	MART	62	21.9 $\pm$ 6.7		23.8 $\pm$ 6.7		24.3 $\pm$ 6.8	
AQLQ Environmental Factors	CONV	58	17.9 $\pm$ 6.7	0.146	19.6 $\pm$ 5.8	0.580	22.6 $\pm$ 4.8	0.766
	MART	62	16.5 $\pm$ 6.3		20.3 $\pm$ 5.4		21.9 $\pm$ 5.7	
AQLQ Total	CONV	58	139.6 $\pm$ 39.5	0.906	160.9 $\pm$ 32.7	0.781	174.0 $\pm$ 31.9	0.969
	MART	62	139.0 $\pm$ 37.6		161.3 $\pm$ 31.6		173.9 $\pm$ 33.1	

In the emotional function section, no significant difference was found in the AQLQ results between the groups at all visits (Table 4). When the groups were compared between visits, a significant improvement was found for the MART group, but no significant improvement was found between visits two and three for the CONV group (Table 5).

A significant difference was found in the AQLQ results between the groups in the environmental stimulants section of the AQLQ ($p > 0.05$; Table 4). Significant improvement in quality of life was found among all three visits in both groups when the visits were compared.

In all sections of the AQLQ, no significant difference in quality of life was found between the devices used ($p > 0.05$).

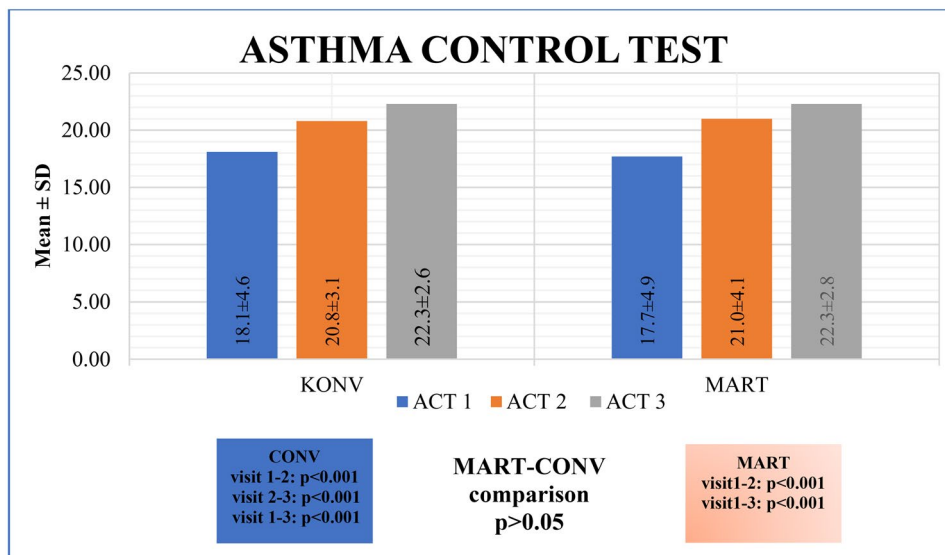
**Figure 1.** Asthma control test between the groups.

Table 5. AQLQ, MGL SCORE, FSI-10, ACT: comparison of groups or devices between visits.

Test	Groups/Devices	visits	p
AQLQ SYMPTOMS	CONV	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
	MART	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
AQLQ ACTIVITY RESTRICTION	CONV	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.007
	MART	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
AQLQ EMOTIONAL FUNCTION	CONV	Visit 1 vs Visit 2	0.002
		Visit 1 vs Visit 3	0.006
		Visit 2 vs Visit 3	0.338
	MART	Visit 1 vs Visit 2	0.032
		Visit 1 vs Visit 3	0.001
		Visit 2 vs Visit 3	0.017
AQLQ ENVIRONMENTAL FACTORS	CONV	Visit 1 vs Visit 2	0.026
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
	MART	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.010
AQLQ TOTAL	CONV	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.001
	MART	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
MGL SCORE	CONV	Visit 1 vs Visit 2	0.007
		Visit 1 vs Visit 3	0.000
		Visit 2 vs Visit 3	0.021
	MART	Visit 1 vs Visit 2	0.000
		Visit 1 vs Visit 3	0.000
		Visit 2 vs Visit 3	0.185
FSI-10	CONV	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	<0.001
	MART	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.272
ACT	Diskus	Visit 1 vs Visit 2	0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.003
	Elipta	Visit 1 vs Visit 2	0.004
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.005
	MDI	Visit 1 vs Visit 2	<0.001
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.043
	Turbuhaler	Visit 1 vs Visit 2	0.004
		Visit 1 vs Visit 3	<0.001
		Visit 2 vs Visit 3	0.028

Relationships between MGL, ACT, FSI-10, AQLQ, and different inhaler techniques

Regarding the relationship between ACT and MGL, a significant relationship was found between the ACT and MGL scores at each visit. There was a significant relationship between the AQLQ and MGL scores at visit one (Table 8).

A significant correlation was found between the FSI-10 and AQLQ scores at each visit and between the FSI-10 and MGL scores at visit one. Furthermore, a significant positive correlation was found between

the FSI-10 and ACT scores at the first two visits, but not at visit three.

Exacerbations

When the patients were seen at the 1st visit; 13 patients in the CONV group and 8 patients in the MART group had an exacerbation in the last 1 year. In the 2nd visit since the last visit; 3 patients in the CONV group and 5 patients in the MART group had an exacerbation. In the 3rd visit, since the last visit; while 2 people in the CONV group had an exacerbation, no one had an exacerbation in the MART group.

Discussion

Several different devices and treatment protocols can be used to treat patients with asthma. The present study concluded that there was no relationship between asthma control and medication adherence with the devices and treatment protocols (MART and CONV) used and that education on inhaler technique at follow-up visits was more important.

Socio-demographic characteristics and comorbidities

Patients' socio-demographic characteristics, comorbidities, and smoking status were homogeneously distributed between both treatment arms, increasing the meaningfulness of the parameters compared.

When the age of the patients and their age at the time of diagnosis were examined, it was seen that some of the patients had received treatment for a number of years. However, as inhaler technique and medication adherence were seen to improve with education and regular follow-up visits, the importance of mentioning these topics at each visit can be seen.

Relationship between patients' adherence and asthma control, satisfaction with their inhaler, and quality of life

The REALIZE study, conducted in 11 European countries, indicated that medication adherence and asthma control were very poor when no special training was given, independent of the given treatment (18). Few studies have compared formoterol/budesonide and formoterol/beclomethasone as maintenance and rescue treatment with conventional treatment in terms of medication adherence and asthma control.

Table 6. MGL Results at the visits.

	Visit 1			Visit 2			Visit 3		
	CONV; (n%)	MART; (n%)	Total; (n%)	CONV; (n%)	MART; (n%)	Total; (n%)	CONV; (n%)	MART; (n%)	Total; (n%)
Non-adherent n (%)	21 (36)	22 (35)	43 (36)	8 (14)	11 (18)	19 (16)	6 (10)	8 (13)	14 (12)
Partially adherent n (%)	20 (34)	32 (52)	52 (43)	27 (47)	29 (47)	56 (47)	20 (35)	24 (39)	44 (37)
Adherent n (%)	17 (29)	8 (13)	25 (21)	23 (40)	22 (36)	45 (38)	32 (55)	30 (48)	62 (52)
Total n (%)	58 (100)	62 (100)	120 (100)	58 (100)	62 (100)	120 (100)	58 (100)	62 (100)	120 (100)
Non-adherent n (%)	12 (55)	9 (25)	21 (36)	3 (14)	5 (14)	8 (16)	5 (23)	2 (7)	7 (12)
Partially adherent n (%)	12 (55)	14 (39)	26 (53)	11 (50)	16 (44)	27 (48)	7 (32)	12 (43)	19 (35)
Adherent n (%)	4 (18)	13 (36)	17 (21)	8 (36)	15 (42)	23 (28)	10 (46)	14 (50)	24 (32)
Total n (%)	22 (100)	28 (100)	50 (100)	22 (100)	36 (100)	56 (100)	22 (100)	34 (100)	56 (100)

In the comparison of CONV and MART groups; It was found as $p=0.052$ at Visit 1, $p=0.805$ at Visit 2, and $p=0.748$ at Visit 3. In the comparison between devices; It was found as $p=0.037$ at Visit 1, $p=0.553$ at Visit 2, $p=0.263$ at Visit 3.

Table 7. MGL SCORE.

		95% confidence interval for mean							Interquartile range
MGL score		Mean	Lower bound	Upper bound	Median	Std. Deviation	Minimum	Maximum	
Visit 1	CONV	1,74	1,34	2,14	1,00	1,52	0,00	4,00	3,00
	MART	2,10	1,74	2,45	2,00	1,39	0,00	4,00	3,00
Visit 2	CONV	1,12	0,81	1,43	1,00	1,19	0,00	4,00	2,00
	MART	1,18	0,88	1,47	1,00	1,17	0,00	4,00	2,00
Visit 3	CONV	0,74	0,47	1,01	0,00	1,04	0,00	4,00	1,00
	MART	0,94	0,64	1,23	1,00	1,17	0,00	4,00	1,25

In the comparison between the two groups using the MWU test, it was calculated as $p=0.141$ in Visit 1, $p=0.738$ in Visit 2, and $p=0.368$ in Visit 3.

Table 8. Correlations between ACT, MGL, and AQLQ at the visits.

		MGL 1	MGL 2	MGL 3
ACT 1	r	0.327	-0.043	0.062
	p	<0.001	0.644	0.501
ACT 2	r	0.164	0.342	0.099
	p	0.073	<0.001	0.283
ACT 3	r	0.037	0.225	0.225
	p	0.692	0.014	0.013
AQLQ 1	r	0.252	0.036	-0.012
	p	0.006	0.698	0.893
AQLQ 2	r	0.098	0.112	-0.099
	p	0.289	0.224	0.281
AQLQ 3	r	-0.021	0.031	0.087
	p	0.817	0.734	0.347

Each comparison included 120 participants.

Rogala et al. (3) divided patients into three groups as follows: beclomethasone/formoterol, fluticasone/salmeterol, or budesonide/formoterol and conducted four follow-up visits over a six-month period. At each visit, it was found that asthma control improved, and the number of the exacerbations decreased, with no significant difference between the groups (3). Kuna et al. (4) compared three groups of patients in terms of respiratory function, asthma control, and quality of life based on their treatment: formoterol/budesonide as maintenance and rescue treatment, salmeterol/fluticasone, and formoterol/budesonide conventionally. Exacerbations occurred less frequently in those using formoterol/budesonide as maintenance and rescue treatment, although no difference was found in quality of life between the groups (4). In the present study, the patients were educated on asthma and inhaler technique/use. We examined whether a significant improvement occurred in medication adherence, asthma control, and quality of life after the patients received training on asthma and inhalers without changing the treatment used. Similarly, our study did not find a significant difference in asthma control and quality of life between the MART and CONV groups.

Papi et al. (19) compared MDI containing beclomethasone/formoterol and Turbuhaler containing formoterol/budesonide. They did not find a difference in recovery in terms of pulmonary function test

results, asthma exacerbations or side effects. In that study, treatment was either LABA/ICS (conventional) or SABA, if required. In our study, MDIs containing beclomethasone/formoterol and Turbuhalers containing budesonide/formoterol were used as maintenance and rescue treatments, and the patients in both groups were compared (19). Similar to our study, Papi et al. did not find a significant difference between the two groups in terms of pulmonary function test results. The AHEAD study (2) compared patients using salmeterol/fluticasone and SABA when required to use budesonide/formoterol as maintenance and rescue treatment. Asthma control and quality of life improved, similar to our study (2). Woodcock et al. (20) conducted the Salford study as a real-life study and randomized patients into two treatment arms as follows: one group used fluticasone/furoate, while the other group continued on their previous treatment. All patients were evaluated using the ACT, MARS medication adherence scale, and AQLQ at their subsequent visits. At the end of the study, medication adherence was seen to increase to 90%. Similarly, in our study, medication adherence increased up to 80% with regular follow-up (20).

Price et al. (21) evaluated patients' satisfaction with their inhaler, medication adherence, quality of life, and respiratory function. Similar to our study, they found a significant positive relationship at each visit between medication adherence and asthma control. However, they did not compare different treatment protocols.

An epidemiological study from America found that 30% of the study participants had well-controlled asthma (22) but could not determine improvement between visits because it was a cross-sectional study. Our study found that 36% of the patients had adequate asthma control at the initial visit. If our study is taken as a cross-sectional study, it may be concluded that we have similar results. However, in our study, patients were followed-up for six months, and asthma control was found to improve over time.

In a study by Janson et al. (23), self-management of asthma improved asthma control and decreased

the number of exacerbations and visits by emergency services. Similarly, we found that education on asthma and inhaler use improved asthma control (23).

Hozawa et al. (24) compared two groups of patients using budesonide/formoterol as maintenance and rescue treatment and fixed-dose fluticasone/vilanterol and SABA as required in terms of asthma control and FeNO values. They found that asthma control and inhaled FeNO levels at weeks zero, two, and four were better in the group using formoterol/budesonide. In contrast, our study did not find a significant difference in asthma control between the groups using formoterol/budesonide and fluticasone/vilanterol (24).

Differences between the devices in terms of asthma control, quality of life, and medication adherence

Janežič et al. (5) compared the Diskus, Turbuhaler, MDI, and Twisthaler devices in terms of medication adherence, asthma control, number of exacerbations, and quality of life. They concluded that misuse occurred more frequently in the group that used the Diskus device and that medication adherence was better with the Diskus and Twisthaler devices than with the MDI and Turbuhaler devices. No significant difference was found in the quality of life scores between those using MDI, Diskus, and Turbuhaler devices (5). In contrast to our study, they did not perform a prospective follow-up and planned their study as a cross-sectional study. Similar to our study, they found that medication adherence was lowest for the Diskus device, followed by the MDI, Turbuhaler, and Ellipta devices before training was given. However, after training had been given, medication adherence improved for all devices, and the difference among the devices disappeared. In our study, improvement in inhaler technique in the CONV arm after training included patients using the Diskus device. The fact that the difference between the devices disappeared at the last visit may be attributed to the fact that the patients that achieved the greatest improvement in inhaler technique were those using the Diskus device with the poorest medication adherence.

In the study by Aggarwal et al. (25) concluded that asthma control was better with the MDI device, but there was no difference between the two devices (MDI and dry powder devices) in terms of treatment satisfaction. In our study, no statistically significant difference was found in treatment satisfaction, although the FSI-10 scores were lower compared to other types of dry inhaler devices at each visit. Regarding asthma

control, the ACT scores were lower in patients using MDI devices, although the difference was not statistically significant. In contrast to the study by Aggarwal et al., no significant difference was found in treatment satisfaction between the devices.

Koya et al. (26) determined the use of inhaler devices and asthma control of patients that presented to the hospital and several local pharmacies. Furthermore, they measured adherence using the dosimeter and compared Diskus, MDI, and Turbuhaler devices. The study found that asthma control was correlated with medication adherence and correct inhaler use (26). Similarly, Koya et al. found that the Diskus device was associated with the lowest level of correct inhaler use. They also found that the misuse rate of Turbuhalers was higher than for MDI devices, whereas our study found it was lower. Like our study, they found a relationship between the ACT scores and medication adherence.

Vogelmeier et al. (6) compared patients using budesonide/formoterol as maintenance and rescue treatment with those using salmeterol/fluticasone and SABA as rescue treatments. The number of exacerbations and use of rescue medication was better in the group on formoterol/budesonide. However, they found no significant difference in terms of the symptoms presented, asthma control, and quality of life (6). In our study, the formoterol/budesonide combination was used with the Turbuhaler device in the MART group, and the salmeterol/fluticasone combination was used with the Diskus device in the conventional group. Like Vogelmeier et al., no statistically significant difference was found between the two groups in terms of the symptoms presented, asthma control, and quality of life.

Limitations of the study

As mentioned, our study was the first to compare both treatment protocols and different types of devices in terms of adherence, control, satisfaction, and quality of life. However, the present study was a single-center study carried out in a tertiary-center.

Furthermore, the lack of a control group may be viewed as another limitation. We did not include a control group as we felt that this would be unethical.

Patients more likely to benefit can be also the ones more likely to consent to participate in the study. Since the treatment protocols of the patients were not changed, the patients did not hesitate to participate in the study. There were patients who were excluded from follow-up due to moving or a different health problem.

The primary aim was mainly to compare adherence, and the sample size was calculated according to this purpose. However, since it was seen that there were two different inhaler devices in both groups, they were also compared. A separate sample size was not calculated for this. Therefore, the appropriateness of the number of patients to compare devices can be discussed.

Training on the inhalers could be interpreted as having an indirect effect on the improved parameters because the treatment did not change in the study groups. Only those patients that agreed to complete the surveys and participate in the study were included, and those that did not regularly attend their follow-up visits were excluded. This might have affected the population of patients included in the study. Regarding socio-demographic characteristics, the fact that our study has similar adherence rates and asthma control means that comparisons can be made with other studies worldwide. The study included patients with asthma from tertiary and quaternary centers and those using the Ellipta, Diskus, MDI, and Turbuhaler devices.

Furthermore, the patients included in the study were already using certain medications. We did not ascertain whether they had received training in the past, which could have affected our results. However, as this was a prospective study, and improvements were found in the results between visits, we believe this did not affect our conclusions.

Conclusions

In conclusion, patients with asthma should be given inhaler training at each visit regardless of the inhaler device they use or which treatment protocol they follow (formoterol/ICS as maintenance and rescue or LABA/ICS and SABA as necessary). This is crucial for improving patients' medication adherence, asthma control, and quality of life. No significant difference was found in patients' control, adherence, satisfaction, and quality of life between the two treatment protocols after training.

Conflict of interest

Authors reports that they have no conflict of interest related the submitting work.

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