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Running Title: Step-Down in Asthma Treatment

A STEP-DOWN EXPERIENCE IN ASTHMA TREATMENT: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: According to recent guidelines; patients with controlled asthma who are stable for at least three months and don't have risk factor should be considered for step down.

Objective: To evaluate our step down attempts and affecting factors.

Methods: This study was a retrospective-cohort study of patients with asthma who were followed up in our clinic for at least one year. Sociodemographic, phenotypic, clinical features and number of step-down attempts were recorded from the files. Step down was tried in well controlled patients and considered as successful whether descending step was maintained or a lower step was reached until the last visit.

Results: A total of 239 patients (196 F/43 M) with a mean age of 51.54 ± 15.29 years were included in the study. Step-down attempt was performed in 44.8 % (n =107) of the patients and % 74.8 (n=80) of them were successful. Factors related to failure were lower level of education, allergic comorbidity (p=0.04) and female gender (p=0.04). Risk of failure was 3.45 and 1.84 times higher than university graduates in high school and primary school graduates, respectively. The probability of failure in step down was 3.38 times higher in patients with allergic comorbidity, and it was 3.92 times more likely in women than men.

Conclusions: Our results showed that the step down attempt could be performed in patients receiving treatment from all steps. In addition, treatment of allergic comorbidities and increased level of education, may make a step down attempt more successful.

Keywords: Asthma, Step-down, Comorbidities, Education, Asthma Control

INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic variable expiratory airflow limitation, progressing with respiratory symptoms that may vary depending on time and intensity. Treatment and follow-up of asthma are based on the concept of control which has two components. The first is to control symptoms and the second is to prevent future risks such as exacerbations, persistent airflow limitation and drug side effects. The goal of asthma treatment is to provide these two control components (1).

Treatment of asthma comprises two types of medications; controllers and relievers. Controller medicines target to keep asthma under control through their anti-inflammatory effects and they should be used every day regularly for step 2-5 treatment, and are recommended to be used as needed in step 1-2 treatment. Today, inhaled corticosteroid (ICS) is the most common used and effective controller. Stepwise approach in asthma treatment is a method in which the treatment is adjusted according to the level of control. It is applied in the form of increasing the dose of medication (step-up) in uncontrolled patients, and decreasing the dose of medication (step-down) in well controlled patients (1).

National and international guidelines and strategies recommend reducing treatment one step further in patients who remain under control for three months after asthma control is achieved. The aim of step-down is to find minimum effective dose that provides symptom control and prevents exacerbations. Thus, side effects and treatment costs of drug are minimized (1,2). In addition, step-down allows to simplify the treatment and increase compliance. Although, strategies of when to consider step down are well defined in the

guidelines, the process in real life is not always precise due to the variations from patient to patient. Because of some potential barriers to successful step-down and lack of data about the factors related to success or failure, physicians may refrain from stepping down (1,3-5).

The objective of this study is to examine our step-down attempts in the asthma follow-up outpatient clinic and evaluate the success of step down attempts and the influencing factors.

METHODS

Study design

The study was planned as a retrospective cohort study in accordance with the Declaration of Helsinki. The study protocol was approved by Local Ethics Committee (Cod: I2-116-20). All files with at least one year of recording were retrospectively evaluated, for up to three years, after patient's permission was obtained.

Study group and data recording

All patients who were followed up in our clinic for at least one year with the diagnosis of asthma according to the GINA criteria, and allowed their files to be examined were included in the study. Sociodemographic (age, gender, smoking habit, educational status, body mass index (BMI)) and phenotypic (atopy, eosinophilia, age of asthma onset) features, presence of allergic (allergic rhinitis, food allergy, urticaria, latex allergy, atopic dermatitis) and/or systemic comorbidities (hypertension, diabetes mellitus, coronary artery disease, thyroid diseases, anxiety-depression, migraine, renal failure, and gastroesophageal reflux), treatment steps at the beginning and the end of the follow-up, number of step-down attempts and the success rates were recorded from the files. The asthma severity of the patients was determined according to the basal treatment steps. Patients with steps 1 to 2 treatment were recorded as mild asthma, step- 3 treatment as moderate, and subjects with step 4 to 5

treatment as severe asthma. In addition, duration of follow up in our clinic, number of visits/per year and its regularity, and asthma medication use patterns were documented.

In our routine, patients are informed about the disease by the physician in the first visit and trained by the nurse not only with printed material and verbal information, but also with demo inhaler devices at each visit. Appropriate usage of inhaler devices was checked according to the inhaler use checklist and also action plans were given. This application is standardized, but is repeated according to the needs of the patients due to individual differences.

Patients with a positive skin prick test result or a positive spIgE measurement for at least one inhalant allergen in the panel were defined as atopic. In the past one year if at least one of the three absolute eosinophil measurements reached $\geq 150/\mu\text{L}$ under oral corticosteroids, $\geq 300/\mu\text{L}$ during oral corticosteroid free period, these patients were classified as having eosinophilic asthma (1,6).

The control status of asthma was determined by physicians as well controlled, partially controlled or uncontrolled according to the ACT score, clinical and functional evaluation with GINA control criteria and pulmonary function tests at the last visit. In addition, the number of asthma exacerbations, emergency admission, additional systemic steroid use or hospitalization history in the last one year period were also considered. Patients with ACT score ≥ 20 and without a history of exacerbation in the last year and had stable pulmonary functions (no more than 12% change in FEV1) were considered as well controlled asthma. If one of these three criteria was not achieved, the patient was accepted as partially controlled and if no criteria were met the patient was classified as uncontrolled.

Evaluation of step-down attempts

Step down attempts were applied to the patients with well controlled asthma according to decision of the physician at the visit. The number of step-down attempts was noted for each

patient. We named the concept of step-down in the treatment in two different ways. First, if the attempt to reduce beclomethasone equivalent ICS dose resulted in a reduction in the treatment step, this was defined as *step-down*. However, if it did not cause a change in the treatment step, the decrease in the dose of beclomethasone equivalent ICS was defined as *in-step dose reduction*. (Table-1) The step-down attempt was considered successful if the descending step was maintained or a lower step was reached at the last visit. However, if the treatment step was increased at any time between the day of step-down attempt and the last visit, it was considered unsuccessful.

Statistical analysis

Statistical analyzes were performed using SPSS version 21 software (SPSS Inc., Chicago, IL, USA). The normality of distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). Quantitative data with normal distribution were presented with mean $\pm$ standard deviation and non-normally distributed numeric variables were presented with median and interquartile range. Categorical variables were summarized with frequencies and percentages. The importance of the difference according to means between the groups examined with Student's t test. Categorical data between the groups were evaluated by Chi-square test, risk analysis was performed in two by two tables and adjusted Odds Ratios were calculated by using Logistic Regression analysis. All directional p values were two-tailed and values less than 0.05 were considered significant.

RESULTS

A total of 239 patients (196 F/43 M) with a mean age of 51.54 ± 15.29 years were included in the study. Nearly half of the group graduated from high school or University. If we looked at the educational status of women and men separately, 48.5% of the women (n = 95) and 69.8% of the men (n = 30) had high school or higher education. Most of them have

adult onset asthma and the mean ACT score was 22.8 ± 3.53 . One hundred and eleven subjects (46.4%) were atopic and 39.3% of the subjects were eosinophilic. The frequency of obese and overweight patients was high and the mean BMI of our study group was 29.29 ± 5.18 . Comorbidities, either allergic or systemic were common in our group with the percentage of 56.1 and 69.9, respectively. In general, subjects used their controller medication regularly, had regular follow-ups (81.6%) and a great majority of them (88.7%) had at least 3 years of follow-up time. (Table-2).

A total of 121 (50.63%) patients were classified as well-controlled asthma. Step down was tried in 107 (44.8%) well controlled subjects. While in the rest of them ($n=14$, 5.85%) step-down could not be attempted due to denial, not feeling ready, or fear of losing control. The mean age (50.87 ± 18.11 year), BMI (29.76 ± 5.5) and ACT score (23.22 ± 3.2) of these 107 patients were similar to the general group. Almost all of them (89.7%) were followed up for at least three years, 86.9% ($n = 93$) stated that they used their controller medication regularly and 84.1% ($n = 90$) of them came to regular follow-up visits in the last year (Table-2). Among these 107 patients, we either made a step down attempt or in-step corticosteroid dose reduction in 63.5% ($n=68$) and 18.7% ($n=20$) of the subjects, respectively. In the rest of the patients (17.7%, $n=19$) we first tried in-step inhaler corticosteroid dose reduction and than treatment step down at consecutive visits (Table-3). The mean number of step-down attempts was 1.5 ± 0.7 and the mean period of well control for these 107 patient was 7.46 ± 3.14 months.

According to the treatment steps, step-down attempt was performed mostly in patients with step-4 treatment followed by step-5, step-2, and step-3 with the trial rates of 1.63, 1.53, 1.38, 1.35 times, respectively. In patients with low treatment step (step-2, step-3) in-step dose reduction was most preferred while, in patients with step-4 and 5, step-down was performed more frequently ($p<0.0001$).

Patients that we did not try step down, had more systemic comorbidities than the others [78% (n=103), 59.8% (n=64), respectively, $p=0.002$]. The proportion of patients attempting step-down was lower in NSAID-sensitive ones and those with nasal polyposis than the patients without NSAID sensitivity or nasal polyposis [for NSAID sensitivity: 31.4%, 48.4%, respectively, ($p=0.02$); for nasal polyposis: 23.3%, 49.5%, respectively, ($p=0.001$)]. In addition, a step-down approach was 14.4 % less common in patients with GERD ($p=0.02$). Phenotypic specialities (atopy, eosinophilia, the age of asthma onset) and the severity of asthma did not affect the rate of step-down attempts (Table-2).

Step-down was successful in 74.8% (n=80) of patients and was maintained for a mean of 15.94 ± 9.44 months. Among these patients, in the vast majority, the treatment step could be reduced in 66.2%, 7.5%, 2.5%, one, two or three steps, respectively and maintain its decreasing trend. The proportion of the patients who were successful in-step dose reduction was 23.8%. (Figure 1). When evaluated according to severity of asthma the success rate was not different in patients with mild, moderate and severe asthma. (77.5%, 70% and 75.6%, respectively. ($p>0.05$).

Education, allergic comorbidities and gender were factors affecting the success rate (Table-4). It was observed that the success rate decreased as the education level decreased. In terms of the risk of failure, the risk was similar among primary and high school graduates (RR:0.91, 95% CI 0.41-2.02), and lower in university graduates. Compared to university graduates, the risk of failure in step down attempt was 1.84 times higher in primary school graduates and 3.45 times higher in high school graduates. [(OR: 1.84, 95% CI 0.54-6.25) ($p=0.42$), (OR:3.45 95% CI 0.82-14.50) ($p=0.21$), respectively].

Step down attempt was found to be more successful in patients without allergic comorbidity than patients with allergic comorbidity. (84.2%, 66.1%, respectively, $p=0.04$) (Table-4). Failure was 3.38 times more likely in patients with allergic comorbidity. (OR: 3.38,

95% CI 1.14-10) ($p=0.04$) Finally, the rate of those who succeeded in step down attempt was higher in men than in women. (93.3 %, 71.4%, respectively) ($p=0.04$) (Table-4) It was noted that women were 3.92 times more likely to be unsuccessful in step-down attempt. (OR= 3.92, 95%CI 0.46-33.3) ($p=0.04$). (Figure-2)

DISCUSSION

Our study has demonstrated that in patients with well controlled asthma, regardless of its severity, step down can be tried and mostly achieved. We attempted to step down especially in patients who came to regular controls and used inhaler treatment regularly. However, our results showed that patients with systemic comorbidities, NSAID sensitivity, nasal polyposis, and GERD had a lower rate of step down attempt. The overall success rate in our step-down attempts was 74.8%. Despite being well controlled, lack of education, female gender and having allergic comorbidity were failure factors.

It is suggested that specialists do not tend to step down in daily practice due to the fear of losing control. In a multicentre retrospective study from Spain, 226 clinicians were reported to have performed step down in only 374 patients per year. Roughly proportionate, this means that a clinician tries to step down in only one to two patients per year (4). Another study investigated the safety and cost-effectiveness of step down in patients with well controlled asthma similar to our study. They reported the rate of the treatment dose reduction as 29.9% (5). However, we achieved a higher rate of step-down attempt in patients with well controlled asthma when compared with these findings. The fact that our study population was followed in a specialized asthma follow up clinic with regular visits may explain the higher rate and success of stepping down in this study. The other side of the coin is that patients also worry about losing control. In this study, a small proportion of the patients (5.85%) were worried about stepping down despite being well-controlled because they did not feel ready. It

seems that doctors' and patients' fear of losing control is one of the major challenges of stepping down.

Long-term and regular follow-up and regular use of medication are associated with adherence to the treatment, which was particularly high in patients we tried to step down. In a one year follow up study from UK, in the medium-dose ICS-LABA group, the rate of step down was 19.0% in all patients and 28.9% in treatment-adherent patients, while these rates were 26,1% and 32,6% in high-dose ICS-LABA cohort, respectively (7). Low adherence to treatment among individuals with asthma has been reported to be associated with poor control in several studies (8,9). Based on this, the high rate we achieved in step down attempts may be related to the adherence of our patients to the treatment.

It has been shown that the presence of systemic comorbidities complicates asthma control and management. In a retrospective study designed to determine the long-term consequences of step down in asthma, one of the factors associated with asthma exacerbation shortly after step down was defined as the Charlson comorbidity index ≥ 1 (10). In addition, in some previous studies, systemic comorbidities have been shown to negatively affect both eligibility of the patient for step-down attempts and the success of step down (4,7). Loss of control in this group of patients with systemic comorbidities, may lead to more risky results and the use of multiple drugs may impair treatment compliance. Furthermore, it has been shown that patients with nasal polyposis, NSAID sensitivity, and GERD are more likely to have impaired asthma control, and these comorbidities make treatment difficult (4,11,12). In accordance with the literature, we observed that the rate of stepping down was lower in patients with systemic comorbidities in our study group.

In different studies, success rates after step down vary from 22% to 87% (13). Our success rate is close to the upper level of this range. All patients in whom reducing the steps were tried in our clinic met the well control criteria, an ACT score of over 19, no history of

exacerbation in last year, and stable pulmonary functions. Guidelines recommend to consider the future risks and related factors before deciding on a step down (1). In parallel, many studies, have pointed out that the history of exacerbation in the past year, a future risk factor, is a predictor of worsening of asthma after step-down (14-16). The fact that we did not perform a step down attempt in patients with one of the future risk factors, have enabled us to achieve a high success rate.

According to our results, it can be speculated that there is a relationship between education level and step down success. No study shows the direct correlation between step down success and education, but several studies demonstrate that low education has impact on the loss of asthma control (17,18). Although the relationship between education level of the patients and living conditions have not been primarily investigated in this study, it can be suggested that poor educated people have lower socioeconomic conditions. In general low education level and insufficient socio-economic conditions bring along some unhealthy lifestyle behaviors such as physical inactivity, carbohydrate-heavy diet and tobacco use and unhealthy environment such as higher exposure to indoor allergens and pollutants. These unfavorable environmental factors contribute to loss of asthma control. On the other hand socioeconomic conditions take place among the factors influencing adherence to asthma treatment (18). Thus, low education level associated with low socioeconomic conditions lead to impaired asthma control on the one hand and reduce adherence to treatment on the other. Accordingly our data show that, reaching asthma control and success in step down seems to increase as the level of education increases.

Another reason for step down failure was allergic comorbidities, which had a higher risk for failure. The rationality of this result may be that allergic comorbidities contribute to loss of asthma control and impair quality of life, as stated in a large review (19). Similar to our study, some studies show that female gender is a factor associated with failure of step

down (3,10). In our study group, the level of education in women was lower than that of men and in line with this finding success rate in step down attempt was also low in women. We suggest that the level of education has an impact on the success of step down, as discussed previously.

This study has some limitations. Firstly the retrospective design of the study may complicate the assessment of asthma control and step down procedures when compared to a prospective trial. However the criteria of well controlled asthma were well determined and the file records were regular and complete in terms of step down attempts in our study. Therefore, we think that the retrospective design has been partially overcome. Secondly having relatively small sample size due to being a single center trial caused some limitations in this study. In addition, adherence to the treatment, that was effective in providing asthma control, and hence in step down attempt could not be evaluated directly due to the retrospective design of the study. Another point, biomarkers can predict success in stepping down, but this is not clear since different studies have different results (4,14,20,21). Although the value of blood eosinophilia evaluated in our study was not related to step down attempt and success, the fact that other biomarkers such as FeNO and sputum eosinophilia are not measured is a limitation of our study. Our study also has some important aspects. Unlike the literature all patients, regardless of the severity of asthma, were included in our study group to better reflect the general asthma population. Since this is a single-center study, a standard step down protocol was applied in our clinic which has reduced possible bias seen in multi-center studies. Third, this is the first study to show the impact of educational level on step down success.

The step down procedure can be tried in patients receiving treatment from all steps according to the criteria specified in the guidelines. Our results indicate that step down

attempts may be more successful with treatment of allergic comorbidities, and increased level of education among the population.

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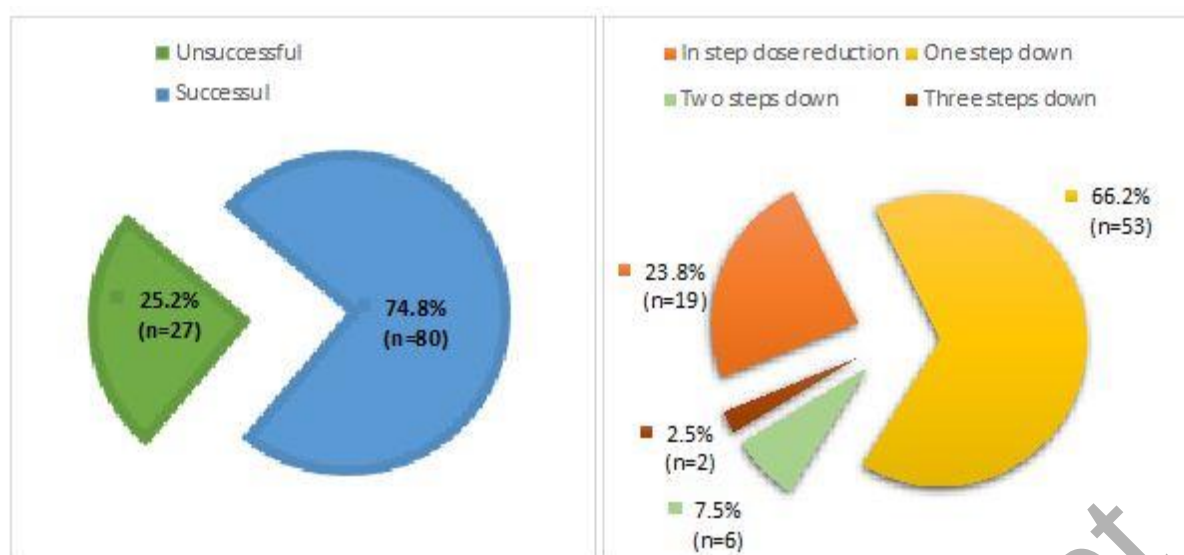


Figure-1 Evaluation of success of patients with step-down attempt. Step-down was successful in 74.8% of patients with one, two or three steps in 66.2%, 7.5% and 2.5% of them, respectively. Success rate of in-step dose reduction was 23.8%.

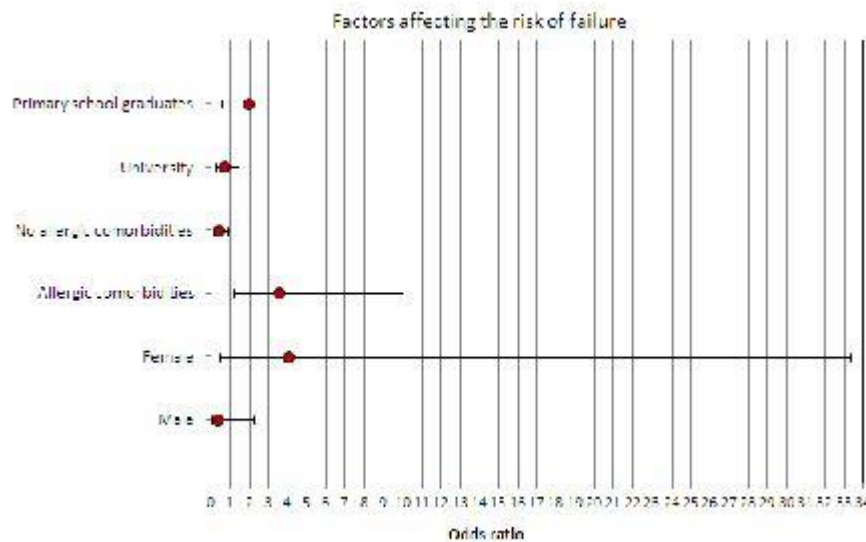


Figure-2 Factors affecting the risk of failure. Primary graduates are at high risk for failure in step down than university graduates. (OR: 1.84, 95% CI 0.54-6.25; OR:0.49 %95 CI: 0.15-0.73, respectively). Having an allergic comorbidity and being women are also risk factors for failure in step down. (OR: 3.38, 95% CI 1.14-10; OR:3.92, 95%CI 0.46-33.3, respectively)

Table 1: In-step dose reduction options

Treatment step	In step dose reduction
Step-5	• Cessation or dose reduction of OCS
Step-4	• Decreasing Budesonide dose from 640 mcg/day to 480mcg/day • Decreasing Beclometazone dose (extrafine particle) from 400mcg/day to 300mcg/day in ICS/LABA combination • Cessation of added different ICS molecule to a ICS/LABA combination
Step-3	• Decreasing Budesonide dose from 320mcg/day to 160mcg/day in ICS/LABA combination • Decreasing Beclometazone dose (extrafine particle) from 200mcg/day to 100mcg/day in ICS/LABA combination • Decreasing Fluticasone propionate dose from 250mcg/day or 200mcg/day to 100mcg/day in ICS/LABA combination
Step-2	• Decreasing Ciclesonide dose from 160mcg/day to 80 mcg/day • Decreasing Budesonide dose from 400 mcg/day to 200 mcg/day or 100mcg/day • Decreasing Fluticasone DPI dose from 250 mcg/day to 125 mcg/day or MDI dose from 200 mcg/day to 100mcg/day or 50 mcg/day
Step-1	• Not available

Table 2: Demographic and phenotypic features of the patients

		Total	Step-down Attempt		p
			Present	Absent	
Gender %(n)	Female	82.0(196)	85(91)	79.5(105)	0.271
	Male	18.0 (43)	15(16)	20.5(27)	
Age mean±SD		51.54 ± 15.29	50.87± 18.11	52.09 ±12.60	0.615
Smoking habit %(n)	NonSmoker	60.7 (145)	63.6(68)	58.3(77)	0.712
	ExSmoker	31.4 (75)	29(31)	33.3(44)	
	Smoker	7.9 (19)	7.5(8)	8.3(11)	
Education status %(n)	Illiterate	3.7 (9)	2.8(3)	4.6(6)	0.840
	Primary school	43.9 (105)	43.9(47)	43.9(58)	
	High school	21.3 (51)	23.4(25)	19.7(26)	
	University	31 (74)	29.9(32)	31.8(42)	
BMI %(n)	Normal (≤24.9)	16.3 (39)	15.9(17)	16.7(22)	0.987
	Overweight (25.0-29.9)	41 (98)	41.1(44)	40.9(54)	
	Obese (≥30.0)	42.7 (102)	43(46)	42.4(56)	
Asthma onset %(n)	Childhood onset (<18y)	9.2 (22)	11.2(12)	7.6(10)	0.460
	Adult onset (18-40y)	52.7 (126)	54.2(58)	51.5(68)	
	Late onset (≥40y)	38.1 (91)	34.6(37)	40.9(54)	
Asthma severity %(n)	Mild	6.7 (16)	56.2 (9)	43.8 (7)	0.227
	Moderate	23.4 (56)	35.7 (20)	64.3 (36)	
	Severe	69.9 (167)	46.7 (78)	53.3 (89)	
Atopy %(n)	Atopic	46.4 (111)	43.9(47)	48.5(64)	0.482
	Nonatopic	53.6 (128)	56.1(60)	51.5(68)	
Blood eosinophilia (≥300 cell/μL) %(n)	Eosinophilic	39.3 (94)	35.5(38)	42.4(56)	0.277
	Non eosinophilic	60.7 (145)	64.5(69)	57.6(76)	
Atopy and eosinophilia %(n)	Atopic and eosinophilic	18.8 (45)	15.8 (17)	21.2 (28)	0.721
Nasal polyposis %(n)	Present	18 (43)	23.3 (10)	76.7 (33)	0.001
	Absent	82(196)	49.5 (97)	50.5 (99)	
NSAID sensitivity %(n)	Present	21.3(51)	31.4 (16)	68.6 (35)	0.021
	Absent	78.7(188)	48.4 (91)	51.6 (97)	
GERD	Present	30.1(72)	34.7 (25)	65.3 (47)	0.028

%(n)	Absent	69.9(167)	49.1 (82)	50.9 (85)	
Allergic comorbidity %(n)	Present	56.1 (134)	52.3(56)	59.1(78)	0.295
	Absent	43.9 (105)	47.7(51)	40.9(54)	
Systemic comorbidity %(n)	Present	69.9 (167)	59.8(64)	78(103)	0.002
	Absent	30.1 (72)	40.2(43)	22(29)	
ACT mean$\pm$SD		22.81 $\pm$ 3.53	23.22 $\pm$ 3.26	22.47 $\pm$ 3.71	0.101
FEV1 %		83.10	84.11	82.10	0.567
Follow-up time %(n)	1 year	5 (12)	1.9(2)	7.6(10)	0.072
	2 years	6.3 (15)	8.4(9)	4.5(6)	
	3 years or more	88.7 (212)	89.7(96)	87.9(116)	
Follow-up %(n)	Regular	81.6 (195)	84.1(90)	79.5(105)	0.365
	Irregular	18.4 (41)	15.9(17)	20.5(27)	
Inhaler medication use %(n)	Regular	83.3 (199)	86.9(93)	80.3(106)	0.173
	Irregular	16.7 (37)	13.1(14)	19.7(26)	
Treatment steps %(n)	Step-1	0.4 (1)	0.9(1)	0(0)	0.125
	Step-2	6.2 (15)	7.5(8)	5.3(7)	
	Step-3	23.4 (56)	18.7(20)	27.3(36)	
	Step-4	30.6 (73)	37.4(40)	25(33)	
	Step-5	39.3 (94)	35.5(38)	42.4(56)	

Table 3: The rates of step-down attempts and preferred methods

	Subgroups	% (n)	Total % (n)
Step-down attempt (-)	No step-down attempt	100 (132)	55.2 (132)
Step-down attempt (+)	Step down	63.5 (68)	44.8 (107)
	In-step dose reduction	18.7 (20)	
	Step-down and in-step dose reduction	17.7 (19)	

Table 4: Comparison of demographic features effective on step-down success

		Step-down Attempt % (n)		p
		Successful	Unsuccessful	
Gender	Female	65 (71.4)	26 (28.6)	0.04
	Male	15 (93.8)	8 (6.2)	
Allergic Comorbidities	Absent	43 (84.3)	8 (15.7)	0.04
	Present	37 (66.1)	19 (33.9)	
Education status	Illiterate	3 (100)	0	0.47*
	Primary school	35 (74)	12 (26)	
	High school	18 (72)	7 (28)	
	University	27 (84)	5 (16)	

* Due to the very low number of illiterate subjects, statistics were made after excluding illiterate subjects.