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Comparison of ICS dose reduction vs. montelukast discontinuation for step-down therapy in well-controlled asthma: a pilot randomized controlled trial

Besharat Rahimi[1], Niloofar Khoshnam Rad[1*], Shahideh Amini[2], Marsa Gholamzadeh[3], Ghazal Roostaei[1], Mahsa Yousefi Mokri[4] and Hamidreza Abtahi[1*]

Abstract

Background While asthma guidelines advocate for reducing inhaled corticosteroid (ICS) doses in well-controlled patients, limited evidence exists to directly support this approach. This study aimed to compare the effectiveness of ICS dose reduction versus montelukast discontinuation as step-down strategies in adults with well-controlled asthma.

Methods This single-center, pilot randomized controlled trial enrolled 73 adults with well-controlled asthma. Participants were randomized to either Group A: ICS Dose Reduction ($n=37$) or Group B: Montelukast Discontinuation ($n=36$). Both groups received standard care and their designated intervention for three months. The primary outcome was asthma control measured by the ACT score. Secondary outcomes included lung function, asthma exacerbation frequency, treatment failure rates, and cough symptoms. Medication adherence was assessed using dose counters and pill counts.

Results There was no significant difference in overall asthma control between the groups, as measured by the ACT score ($p=0.42$). However, patients in Group A (reduced ICS) experienced significantly fewer treatment failures compared to Group B (discontinued montelukast) at three months ($p=0.01$). No serious adverse events were reported.

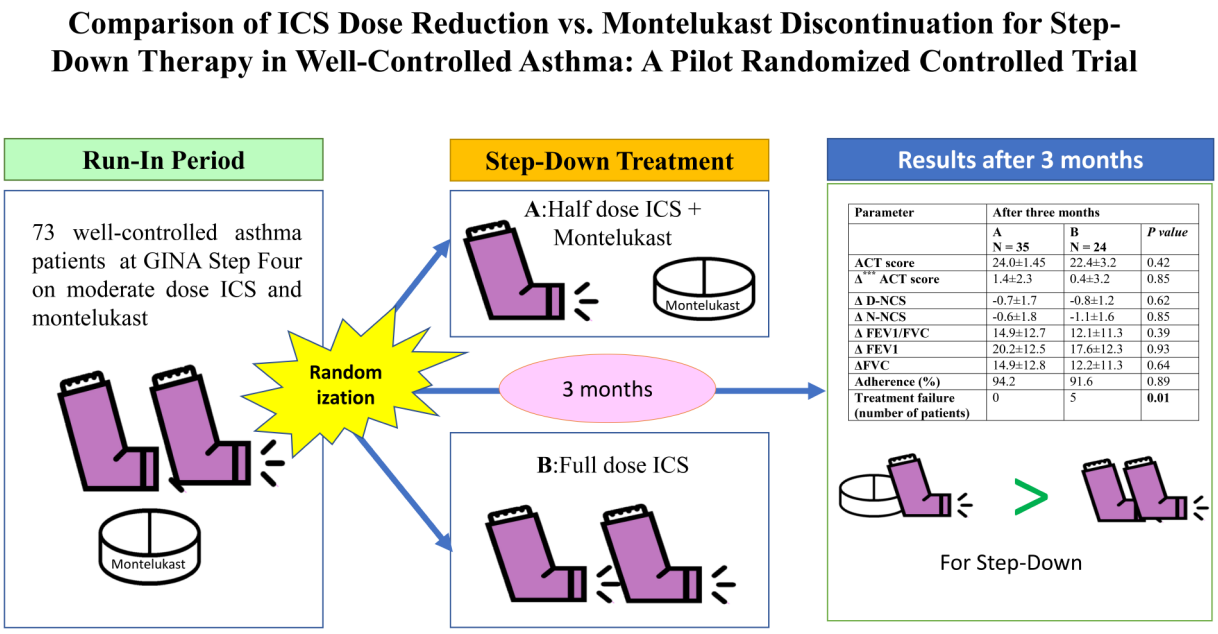
Conclusion Although the ACT scores did not significantly differ between the groups, we did observe a trend towards fewer treatment failures in the ICS reduction group. This suggests that reducing ICS doses may help to maintain asthma control and reduce the risk of exacerbations. However, further research is warranted to confirm these findings in larger, long-term studies.

Trial registration IRCT Registration Number IRCT2016052428037N1, Retrospectively registered, Registration Date 20,160,701.

*Correspondence:
Niloofar Khoshnam Rad
Kh.niloofar@yahoo.com
Hamidreza Abtahi
hrabtahi@sina.tums.ac.ir

Full list of author information is available at the end of the article

Graphical abstract



Keywords Well-controlled asthma, Step-down, Montelukast, Inhaled corticosteroids

Introduction

Asthma is a chronic inflammatory airway disease, affecting an estimated 300 million people globally [1]. Asthma is a heterogeneous disease characterized by chronic airway inflammation, defined by a history of variable respiratory symptoms such as wheezing, dyspnea, chest tightness, and cough. Diagnosis relies on characteristic symptom patterns and evidence of variable expiratory airflow limitation documented through bronchodilator reversibility testing or other objective tests [2, 3].

The primary objective of asthma management aims to control of asthma symptoms, enhance lung function, and minimize the risk of long-term complications. This includes infrequent or absent asthma symptoms, preserving or improving personal best lung function, reducing exacerbations, avoiding maintenance oral corticosteroid (OCS) therapy, and preventing medication side-effects [4].

The stepwise approach to asthma pharmacotherapy involves gradually increasing medication to achieve symptom control and prevent exacerbations, followed by stepping down after several months of good control [2]. While under-treatment is a well-known issue in asthma management, it's important to recognize that over-treatment is also prevalent and can lead to adverse outcomes [5].

These consequences include an increased risk of side effects, high-cost burden, and poor adherence [6]. By reducing or "stepping down" asthma pharmacotherapy, healthcare providers can decrease adverse events and financial burden while improving patient adherence [5]. Moreover, stepping down can help re-evaluate the current asthma diagnosis [2]. The minimally effective dose (the lowest dose that maintains good symptom control and minimizes exacerbation) should align with patient values and preferences [7].

Once good asthma control has been achieved and maintained for 2–3 months, gradual stepping-down treatment to find the lowest effective ICS dose should be considered [2]. Montelukast, an orally administered leukotriene receptor antagonist (LTRA), is recommended in the recent GINA guideline as an option for maintenance therapy in patients whose asthma remains uncontrolled despite ICS use [2]. It is also effective in aspirin-exacerbated respiratory disease (AERD) [8] and in pediatric population [9].

Given montelukast's favorable tolerability, ease of use, and safety profile, some patients and physicians may prefer a trial of adding montelukast to ICS rather than increasing the ICS dosage. This preference is due to concerns about adrenal suppression, growth retardation, and bone loss associated with high-dose ICS therapy [10]. A recent meta-analysis found that montelukast did not significantly increase neuropsychiatric events compared with placebo in patients with allergic airway disease [11]. Considering montelukast's favorable safety

profile compared to high-dose ICS, we examined ICS dose reduction and montelukast discontinuation as step-down strategies in adult patients with well-controlled asthma.

Methods

Participants and study design

We conducted a single-center, randomized controlled trial (RCT) at the Imam Khomeini Hospital pulmonary clinic in Tehran, Iran. Adult patients (≥ 18 years old) with a confirmed asthma diagnosis for at least one year were eligible for inclusion. Participants were required to have well-controlled asthma, as defined by an Asthma Control Test (ACT) score ≥ 20 for at least three months without experiencing any asthma exacerbations in the past year.

Exclusion criteria included pregnancy, current smoking, heart failure, asthma exacerbations requiring hospitalization or systemic corticosteroids within the past three months or during the study period, and pre-existing or medication-induced neuropsychiatric symptoms. All participants provided written informed consent (Ethical code: IR.TUMS.REC.1395.2596). This study was conducted and reported in accordance with the CONSORT guidelines for the reporting of randomized controlled trials. A completed CONSORT checklist is provided as Supplementary Material.

Demographic data, medical history (including asthma duration, triggers, comorbidities, and current medications), height, and weight were recorded.

Well-controlled asthmatic patients (ACT score ≥ 20) on medium/high dose inhaled corticosteroid-long-acting beta-agonist (ICS-LABA) combination therapy and 10 mg daily montelukast (Airokast®, Cobel Darou Pharmaceutical Company) for at least three months (GINA Step 4) were randomized into two groups:

- Group Montelukast: Reduced ICS dose (Montelukast continued) (LABA dose unchanged).
- Group ICS Discontinued Montelukast (ICS dose maintained) (LABA dose unchanged).

Randomization was performed using a computer-generated sequence (by study statistician), with participants allocated to groups via sequentially numbered, opaque sealed envelopes. Patients were not blinded to their treatment group, while the principal investigator and data analyst remained masked to reduce bias. Follow-up visits occurred at one and three months.

Spirometry was conducted at baseline, one month, and three months. Asthma control was assessed using the validated Persian version [12] of the Asthma Control Test (ACT), and cough symptoms were evaluated with the Cough Symptom Score (CCS) at each visit.

ACT questionnaire is a 5-item, patient-administered survey for assessing asthma control. Scores categorize asthma control as well-controlled (20–25), partially controlled (16–19), and very poorly controlled (≤ 15). It has a minimal important difference of 3 points and is validated in many languages, including a valid Persian version used in this study [12–14].

Cough symptom score (CSS) is a validated scoring system (0–5) that evaluates daytime and nighttime cough severity separately [15, 16].

Objectives and outcome measures

The primary outcome was asthma control assessed by the ACT score in both groups. Secondary outcomes included lung function (Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 s (FEV1), FEV1/FVC ratio), asthma exacerbation frequency, treatment failure rates, and standardized questionnaire scores. All outcomes were measured at baseline, week 4 (interim visit), and week 12 (study conclusion).

Medication adherence was assessed using inhaler dose counters and pill counts.

Patients were allowed to use as-needed ICS/LABA agents to control breakthrough asthma symptoms during the study period. If a patient experienced a sustained decline in ACT score below 20, indicating a clinically meaningful deterioration in asthma control, or required emergency room visits or hospitalization, despite using as-needed ICS/LABA agents, it was considered a treatment failure. Patients who experienced treatment failure were excluded from the study and referred to their healthcare provider for further evaluation and adjustment of their asthma management plan.

Sample size and statistical analysis

Based on previous studies (SD of change in ACT scores: 1.3–3.9) [17], we set a superiority margin of 3 and estimated SD as 3 for sample size calculation. With 95% power and 0.005 significance level, 54 patients (27/group) were required. Anticipating a 25% dropout rate, the sample size was increased to 72 (36/group).

Statistical analysis was performed using SPSS 25.0 (IBM). Descriptive statistics summarized participant demographics and clinical characteristics. Continuous variables were presented as mean ± SD or median with IQR, while categorical variables were frequencies and percentages. Normality was assessed using Shapiro-Wilk test and visual inspection.

Group comparisons for continuous variables were performed using independent t-tests (normally distributed) or Mann-Whitney U tests (not normally distributed). Chi-square tests or Fisher's exact tests were used

for categorical variables. The Kolmogorov-Smirnov test compared adherence distribution between groups. Significance level was set at $P < 0.05$.

Changes in asthma control over time were analyzed using repeated measures ANOVA with group as a between-subject factor and time as a within-subject factor (baseline, one month, three months). Post hoc pairwise comparisons with Bonferroni correction assessed differences in asthma control between groups at each time point and within each group over time. Significance level was $P < 0.05$ with Greenhouse-Geisser correction for violated sphericity assumption (Mauchly's test, $P < 0.05$). Effect sizes were calculated as partial eta squared (η^2) for ANOVA and Cohen's d for pairwise comparisons (Hedges' g adjustment for unequal sample sizes).

Results

Patient disposition and characteristics

A total of 100 patients with asthma meeting the inclusion criteria (ACT score ≥ 20) were screened for the study. Of these, 73 patients were enrolled and randomized into two groups: Group Montelukast (ICS dose reduction, $n = 37$) and Group ICS (montelukast discontinuation, $n = 36$). Two patients in Group ICS declined to participate in the study. During the study, five patients were lost to follow-up (two from Group Montelukast and three from Group ICS). Additionally, seven patients in Group ICS were excluded due to treatment failure necessitating a step-up in treatment. The final analysis included data from 59 patients: 35 from Group Montelukast and 24 from Group ICS. Figure 1 illustrates the study flow and the number of patients included in the analysis.

Baseline characteristics

The study included patients with well-controlled asthma on GINA Step Four treatment, all receiving moderate-dose ICS-LABA and montelukast. There were no statistically significant differences in baseline characteristics, including demographic information, initial spirometric parameters, ACT scores, and Cough symptom scores (Table 1).

Medication adherence and safety

Adherence to the medication regimen was high (over 90%) in both groups, with no significant difference in adherence distribution ($P = 0.89$). No serious adverse drug reactions were reported by any participant during the study.

Outcomes

The average ACT Score, daytime and nighttime NCS Score, FVC, FEV1, and FEV1/FVC ratio were measured at one and three months and are presented in Table 2. There were no significant differences between the two groups in these parameters (Table 2). At the end of the study, all patients in Group Montelukast (ICS dose reduction) remained well-controlled (ACT > 20). In contrast, Group ICS (montelukast discontinuation) experienced a higher rate of treatment failures: two patients (6%) experienced treatment failure at one month, and five patients (16%) experienced treatment failure at three months.

Primary outcome: asthma control

A mixed design ANOVA revealed no statistically significant difference between the groups in changes in ACT scores over time ($p = 0.167$).

Secondary outcomes

- Treatment Failure: Treatment failure (a sustained decline in ACT score below 20, along with the need for increased reliever medication or worsening symptoms, as an indicator of treatment failure) was significantly higher in patients who discontinued montelukast ($P = 0.01$). Importantly, none of the patients in either group required emergency room visits or hospitalization due to worsening asthma symptoms.
- Pulmonary Function parameters: There were no significant differences in pulmonary function parameters (FVC, FEV1, FEV1/FVC ratio) between the groups at either one or three months.
- Cough Symptoms: Nighttime and daytime NCS scores remained similar between the groups throughout the study.

Discussion

This pilot randomized controlled trial (RCT) investigated the effectiveness of two step-down strategies in adult patients with well-controlled asthma receiving medium/high-dose ICS-LABA and montelukast (GINA Step 4). Our primary outcome was asthma control assessed by the ACT score. No significant difference in asthma control was observed between the two groups ($p = 0.123$). However, patients in Group Montelukast (reduced ICS) experienced fewer treatment failures compared to Group ICS (discontinued montelukast) at one-month (0 vs. 2, $p = 0.14$) and three months (0 vs. 5, $p = 0.01$) follow-up. While our study did not demonstrate a statistically significant difference in overall asthma control between the two groups, the trend towards fewer treatment failures in the ICS reduction group (0% in Group Montelukast vs. 20% in Group ICS) suggests that this approach may be a viable option for some patients. However, the relatively low failure rate in both groups (9.5% overall) highlights the need for larger studies with longer follow-up periods to confirm these findings and establish the definitive superiority of one strategy over the other.

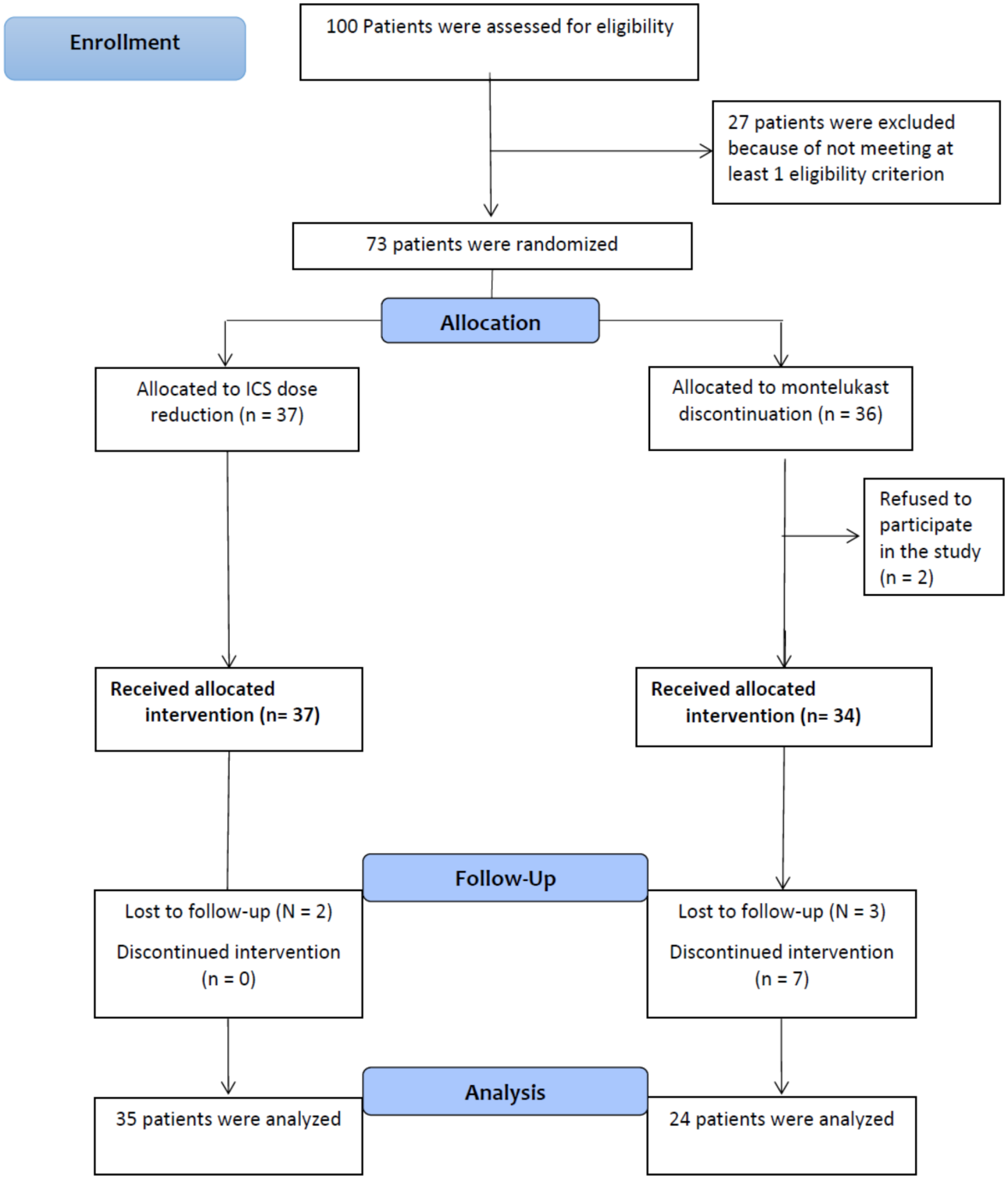


Fig. 1 Patient disposition flowchart for the randomized controlled trial comparing montelukast discontinuation vs. ICS dose reduction in adults with well-controlled asthma

Table 1 Baseline characteristics of the patients examined, grouped based on randomized treatment

Parameter	Group Montelukast (*n* = 37)	Group ICS (*n* = 34)	*P*-Value
Age (years), (mean ± SD)	41.8 ± 13.08	39.1 ± 12.14	0.39
Gender (Female %)	75%	68%	0.57
Marital Status (Married)	68%	78%	0.67
Weight (Kg), (mean ± SD)	71.6 ± 13.99	70.8 ± 14.69	0.81
Height (m), (mean ± SD)	1.65 ± 0.86	1.64 ± 0.11	0.93
Body Mass Index (mean ± SD)	26.3 ± 4.44	25.3 ± 6.6	
Years from asthma diagnosis (mean ± SD)	8.8 ± 6.22	8.17 ± 6.44	0.48*
Allergic conditions	30%	44%	0.20
Gastroesophageal reflux disease	27%	27%	0.99
Diabetes mellitus	2.5%	6%	0.37
Hypertension	2.5%	10%	0.16
ACT score	22.7 ± 1.92	22.45 ± 2.64	0.14*
Daytime-CCS	1.23 ± 1.33	1.34 ± 1.28	0.50*
Night time-CCS	1.35 ± 0.73	1.50 ± 1.14	0.16*
Pre-FVC (% predicted)	79.36 ± 13.26	84.76 ± 17.48	0.17
Pre-FEV1 (% predicted)	70.62 ± 16.69	73.28 ± 15.08	0.53
FEV1/FVC (Pre)	81.19 ± 14.84	75.47 ± 10.19	0.10

Group Montelukast: Half dose of their ICS + montelukast

Group ICS: Full dose of their ICS without montelukast

Allergic conditions includes hives, allergic rhinitis, and/or allergic skin conditions

Abbreviations: ACT score = Asthma Control Test score, FVC = Forced vital capacity, CCS = Cough symptom score, Pre-FEV1 = Pre bronchodilator forced expiratory volume in 1 s

*Mann-Whitney U Test

Our results align with the GINA 2024 recommendation of reducing the ICS dose while continuing the second controller in patients at Step 4 treatment [18].

Evidence from previous studies

Two recent systematic reviews [19, 20] have shed light on the role of LTRAs in asthma management. Zhu et al. (2023) [20] found that adding montelukast to standard therapy with ICS and LABAs improved asthma control and lung function in adults with cough-variant asthma (CVA). However, Chauhan et al. (2017) [19] did not support the use of LTRAs as a complete replacement for ICS, even though they demonstrated benefits when used in combination with ICS. A recent study by Wang et al. (2024) demonstrated the benefits of combining montelukast with budesonide/formoterol in patients with obstructive airway diseases. The combination therapy led to improved symptom control, enhanced lung function, and reduced inflammation compared to budesonide/formoterol alone. Notably, this benefit was achieved without increasing the risk of adverse events [21]. The combination of montelukast and fluticasone propionate has shown promise in the treatment of cough variant asthma (CVA) in children. A recent meta-analysis by Wei and Li (2023) demonstrated that this combination therapy was more effective than fluticasone propionate alone in improving symptom control, reducing cough recurrence, and accelerating symptom resolution. Additionally, the combination therapy led to significant improvements in lung function. These findings suggest that the addition of montelukast to fluticasone propionate may be a valuable strategy for managing CVA in pediatric patients [22].

Table 2 Asthma control outcomes in different treatment phases– ICS taper with montelukast continuation vs. montelukast discontinuation without ICS taper

Parameter	Baseline			After one month			After three months		
	A* *N* = 37	B** *N* = 34	*P* value	A* *N* = 35	B** *N* = 29	*P* value	A* *N* = 35	B** *N* = 24	*P* value
ACT score	22.7 ± 1.92	22.45 ± 2.64	0.14	23.3 ± 1.7	23.5 ± 1.8	0.43	24.0 ± 1.45	22.4 ± 3.2	0.42
Δ*** ACT score	-	-	-	0.7 ± 1.73	1.3 ± 2.4	**0.02**	1.4 ± 2.3	0.4 ± 3.2	0.85
D-NCS	1.23 ± 1.33	1.34 ± 1.28	0.50	0.7 ± 0.5	0.8 ± 0.8	0.40	0.6 ± 0.9	0.5 ± 0.5	0.61
Δ D-NCS	-	-	-	-0.5 ± 1.2	-0.5 ± 1.1	0.78	-0.7 ± 1.7	-0.8 ± 1.2	0.62
N-NCS	1.35 ± 0.73	1.50 ± 1.14	0.16	0.3 ± 0.2	0.4 ± 0.7	0.26	0.3 ± 0.3	0.2 ± 0.4	0.17
Δ N-NCS	-	-	-	-0.4 ± 1.5	-0.7 ± 1.4	0.83	-0.6 ± 1.8	-1.1 ± 1.6	0.85
FEV1/FVC (%)	81.19 ± 14.84	75.47 ± 10.19	0.10	87.5 ± 11.7	85.2 ± 9.8	0.27	84.9 ± 10.1	88.6 ± 7.61	0.56
Δ FEV1/FVC	-	-	-	7.7 ± 13.3	9.5 ± 10.4	0.33	14.9 ± 12.7	12.1 ± 11.3	0.39
FEV1	70.62 ± 16.69	73.28 ± 15.08	0.53	85.6 ± 10.4	84.5 ± 10.8	0.85	91.5 ± 8.8	86.9 ± 6.1	0.14
Δ FEV1	-		-	14.8 ± 11.6	13.8 ± 10.9	0.85	20.2 ± 12.5	17.6 ± 12.3	0.93
FVC	79.36 ± 13.26	84.76 ± 17.48	0.17	89.6 ± 10.9	89.3 ± 10.1	0.68	95.0 ± 10.0	91.5 ± 6.14	0.35
ΔFVC	-	-	-	9.5 ± 8.6	9.1 ± 11.9	0.08	14.9 ± 12.8	12.2 ± 11.3	0.64
Adherence (%)	100	100	-	97.1	100	0.88	94.2	91.6	0.89
Treatment failure (number of patients)	-	-	-	0	2	0.14	0	5	**0.01**

*A: ICS taper with montelukast continuation, **B: Montelukast discontinuation without ICS taper, ***Difference from baseline

Abbreviations: ACT score = Asthma Control Test score, D-CSS: Daytime Cough Symptom Score, FVC = Forced vital capacity, N-CSS: Nighttime Cough Symptom Score, SD = standard deviation, FEV1: forced expiratory volume in 1 s

Our study aligns with these findings by suggesting that reducing the ICS dose while continuing montelukast might be a more favorable step-down strategy compared to discontinuing montelukast altogether. This approach potentially balances the benefits of LTRAs for asthma control with minimizing the side effects associated with high-dose ICS. It is important to note that the effectiveness of LTRAs might vary depending on the specific asthma phenotype. Further research is needed to identify patients who are most likely to benefit from LTRA therapy. Additionally, the increased risk of serious adverse events observed by Chauhan et al. [19] when tapering ICS while adding LTRAs warrants caution. Healthcare providers should carefully weigh the potential benefits and risks for each individual patient before making treatment decisions.

Several studies have demonstrated the effectiveness of montelukast in facilitating ICS tapering and maintaining asthma control. In a study by the American Lung Association Asthma Clinical Research Centers, patients with well-controlled asthma on twice-daily fluticasone were successfully transitioned to step-down treatment with once-daily fluticasone plus salmeterol. Notably, patients receiving montelukast experienced fewer symptoms on 78.7% of treatment days after 30 days [23]. However, our study differed in that we stepped down the treatment of patients rather than switching it. Furthermore, our patient population had more severe asthma compared to those in the mentioned study [23], who had mild asthma.

Price et al. (2001) conducted a large open-label study demonstrating that adding montelukast significantly facilitated tapering of ICS in patients with chronic asthma. The study found a substantial reduction in mean ICS dose (over 80%) while maintaining asthma control. Importantly, a significant portion of participants (nearly 60%) were able to completely discontinue ICS use by the end of the study [24]. It is worth noting that current guidelines generally do not recommend completely discontinuing ICS in patients with asthma. Even after achieving well-controlled asthma, a low-dose ICS regimen may be necessary to maintain long-term control and prevent exacerbations [2].

Riccioni et al. (2005) conducted a randomized controlled trial investigating the effectiveness of montelukast in tapering budesonide inhaler in patients with mild-to-moderate asthma. The study found that patients receiving montelukast alongside budesonide experienced a significantly greater improvement in lung function compared to those receiving budesonide alone. Both groups were able to successfully taper their budesonide dose without compromising asthma control [25].

Given these findings and the results of our studies, we advise against discontinuing montelukast therapy in patients who are well-controlled on both montelukast and ICS-LABA. This recommendation is particularly important for patients with more severe asthma, as they may not respond as favorably to a step-down treatment approach without montelukast.

Rationale for the study design

The recent GINA guideline recommends medium-dose ICS-LABA as the preferred Step 4 treatment [18]. LRTAs are among the options that can be added to medium or high-dose ICS [18]. Our study focused on comparing ICS dose reduction with montelukast discontinuation while maintaining LABA dosage. This design was chosen because discontinuing LABA could lead to poor asthma control [26, 27]. The as-needed ICS-Formoterol strategy could be advantageous in avoiding treatment with short-acting beta 2-agonist (SABA), and thus, maintaining a low-dose ICS-formoterol plus montelukast could potentially benefit patients by providing them with a single controller and reliever medication, thereby increasing their adherence [18]. Our study aimed to explore the feasibility and effectiveness of reducing ICS doses in well-controlled asthma. Previous research has demonstrated that most of the benefits of ICS are achieved at low doses with minimal side effects [28, 29]. By reducing ICS doses, we hypothesized that we could potentially minimize the risk of adverse effects associated with high-dose ICS therapy.

Step-down strategies should be tailored to individual patient needs. While sputum eosinophil count and FeNO-guided approaches have been explored, their use is limited by accessibility and lack of clear benefit compared to standard care [18, 30–33]. In this study, we based the step-down decision on individual factors and physician judgment. We included participants with well-controlled asthma for at least three months, defined by an ACT score ≥ 20 and no exacerbations in the past year. This selection process aimed to identify patients most likely to benefit from a step-down approach.

Regarding treatment failure, patients were allowed to use as-needed ICS/LABA agents to control breakthrough symptoms during the study period. This approach allowed us to assess the effectiveness of the step-down strategies in real-world clinical practice, where as-needed ICS/LABA agents are often used to manage breakthrough symptoms. By including the option of as-needed ICS/LABA use, we were able to evaluate the strategies under more realistic conditions. However, if a patient required emergency room visits or hospitalization due to worsening asthma symptoms, it was considered a treatment failure. It is important to note that seven cases of treatment failure in our study involved patients with ACT scores below 20 who did not require emergency care. These patients were able to regain control of their asthma symptoms by returning to their previous

medication dosages. This highlights the importance of closely monitoring patients for worsening symptoms, even in the absence of severe exacerbations. By identifying and addressing deteriorating asthma control early, it may be possible to prevent more severe outcomes and avoid the need for hospitalization.

Balancing ICS benefits and risks

Understanding the dose-response relationship of ICS is crucial for optimizing asthma management. Recent studies have highlighted the non-linear nature of this relationship, suggesting that there is a plateau beyond which increasing the dose may not provide significant additional benefits [34, 35]. This implies that excessive dosing can be avoided by carefully considering the individual patient's needs and tailoring the ICS dose accordingly.

Beasley et al. proposed a "standard daily dose" for ICS, which corresponds to the dose that achieves approximately 80–90% of the maximum therapeutic benefit. This could help guide prescribing practices and avoid excessive dosing [35].

While the study on ICS/fast-onset LABA reliever therapy suggests that higher doses might be necessary for optimal efficacy in reducing severe exacerbations [36], individual variability in the dose-response relationship of ICS is also crucial to consider. Factors such as asthma severity, comorbidities, and adherence to treatment can influence the optimal ICS dose [35]. Therefore, a personalized approach to asthma management is essential.

Long-term high-dose ICS is associated with an increased risk of local and systemic side effects, including adrenal suppression, diabetes, cataracts, glaucoma, osteoporosis, and bone fractures. Additionally, high-dose ICS therapy can lead to poor adherence due to the inconvenience of frequent dosing and the potential for side effects [37, 38].

Gradually stepping down ICS doses by 25–50% at three-month intervals is recommended by GINA guidelines specifically for patients receiving medium or high doses of ICS plus a second controller [18]. Lowering the ICS dose may reduce the risk of these adverse effects while maintaining asthma control [37].

Our findings support this approach, suggesting that reducing the ICS dose while maintaining montelukast may be a safer and more effective step-down strategy compared to discontinuing montelukast. This approach aligns with the current understanding of the dose-response relationship of ICS and the importance of minimizing the risk of adverse effects while maintaining asthma control.

Our study explored the feasibility of reducing ICS doses in well-controlled asthma patients. However, it's important to acknowledge that reducing ICS doses can increase the risk of exacerbations, particularly in patients with severe asthma or a history of frequent exacerbations. Therefore, a cautious and gradual step-down approach, combined with close monitoring, is crucial to minimize this risk. Moreover, excessive reliance on systemic corticosteroids can lead to significant adverse effects, including cardiovascular events, diabetes, and infections [39]. Optimizing inhaled therapy, such as ICS and long-acting beta-agonists, is essential to maintain asthma control and reduce the need for systemic corticosteroids, ultimately improving patient outcomes.

Neuropsychiatric adverse events associated with montelukast

As noted in the montelukast monograph and highlighted by the U.S. Food and Drug Administration (FDA) boxed warning, neuropsychiatric events, ranging from mild symptoms like anxiety and insomnia to more severe manifestations such as hallucinations, suicidal thoughts, and aggressive behavior, have been reported in patients of all ages taking montelukast [40]. While a 2023 systematic review did not find a direct association between montelukast and suicide or depression-related events, it is important to acknowledge that the risk of such events may vary among individuals [41]. Factors like age, underlying mental health conditions, and concurrent medications can influence susceptibility [41].

Our study did not observe any neuropsychiatric adverse effects among the participants. However, given the potential for individual variability and the limitations of our study's sample size and duration, ongoing monitoring for neuropsychiatric symptoms in patients taking montelukast is recommended, especially in those with risk factors or a history of mental health conditions. Healthcare providers should be vigilant in reporting any suspected adverse events to regulatory authorities.

Limitations and future directions

The findings of this study should be interpreted in light of the following limitations:

- **Patient population**: The study focused on well-controlled asthma patients receiving moderate-dose ICS. This may limit the generalizability of the findings to patients with severe asthma or those requiring higher ICS doses, or those who are not controlled with ICS-LABA and montelukast alone. Additionally, the study did not include patients receiving LAMA or biologic therapy, which are often used for more severe asthma.
- **Cost considerations**: While montelukast was relatively inexpensive in our country, it can be costly in other regions. This may limit the accessibility of LTRAs and influence the choice of step-down strategy.

- **Study duration**: The three-month follow-up period was relatively short and may not have captured the long-term effects of step-down strategies on asthma control and exacerbation rates.
- **Single blind design**: The study was not double-blinded due to the inherent differences between montelukast and ICS. While single-blinding can help to minimize bias, it is possible that patients' knowledge of their treatment assignment may have influenced their self-reported outcomes. Future studies could explore alternative methods to mask the treatments, such as using placebo inhalers or double-blinding the data analysis process, to further reduce the potential for bias.
- **Statistical power**: The study was powered to detect a moderate effect size with 80% power. However, the smaller sample size, particularly at the 3-month follow-up, may have limited our ability to detect smaller but clinically significant differences between the groups, especially for secondary outcomes. To definitively determine the optimal step-down strategy for asthma management, larger, adequately powered studies are needed.
- **Lack of non-inferiority or equivalence margin**: As a superiority trial, we did not define a non-inferiority or equivalence margin a priori. This could have influenced the interpretation of the findings, particularly if the differences between the groups were small but clinically meaningful [42].
- **Hawthorne effect**: While our study aimed to investigate the effectiveness of step-down strategies in well-controlled asthma, it is important to acknowledge the potential influence of the Hawthorne effect, where participants may experience improvements due to increased attention and monitoring rather than the specific interventions [43]. To minimize this bias, we employed a rigorous study design and standardized outcome assessments. However, the possibility of a Hawthorne effect cannot be entirely excluded.

Future multi-center studies should address these limitations to provide a more comprehensive and robust understanding of the optimal step-down strategies for asthma management. Additionally, future studies could explore the use of biomarkers to identify patients who may benefit most from specific step-down strategies and to monitor treatment response.

Conclusion

Our study evaluated the effectiveness of step-down strategies in well-controlled asthma patients. While reducing ICS doses may be feasible for some patients, maintaining montelukast therapy may be beneficial, especially for those with severe asthma or a history of frequent exacerbations. Larger studies are needed to confirm these findings and guide optimal step-down strategies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03629-6.

Supplementary Material 1

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Author contributions
B.R.: Conceptualization, Methodology, Project administration, Writing- review and editing; N.K.: Formal analysis, Investigation, Methodology, Validation, Writing– original draft, Writing– review & editing; S.A.: Data curation, Investigation, Project administration; M.G.: Formal analysis, Writing- review and editing; G.R.: Writing– original draft, Writing– review & editing; M.YM.: Methodology, Writing– review & editing; H.R: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing– review & editing.

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Data availability
The data that support the findings of this study are available from the corresponding author, [H.A.], upon reasonable request. Restrictions apply to the availability of these data due to privacy and confidentiality concerns.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Research Ethics Committee of Tehran University of Medical Sciences (TUMS) (Ethical code: 94-03-159-30560). Written and verbal informed consent was obtained from all participants prior to their enrollment in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Clinical trial registration
The study was registered at IRCT.ir (Registration Code: IRCT2016052428037N1, Registration date: 2016-07-01). (https://en.irct.ir/trial/22836).

Author contribution statement
B.R.: Conceptualization, Methodology, Project administration, Writing- review and editing; N.K.: Formal analysis, Investigation, Methodology, Validation, Writing– original draft, Writing– review & editing; S.A.: Data curation, Investigation, Project administration; M.G.: Formal analysis, Writing- review and editing; G.R.: Writing– original draft, Writing– review & editing; M.YM.: Methodology, Writing– review & editing; H.R: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing– review & editing.

Author details
[1]Thoracic Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[2]Rajaie Cardiovascular Medical and Research Institute, Tehran, Iran
[3]Health Information and Medical Informatics Department, Tehran University of Medical Sciences, Tehran, Iran

[4]Department of Pharmacy, Uppsala Biomedical Center, Uppsala University, P.O. Box 580, SE-751 23 Uppsala, Sweden

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