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ORIGINAL RESEARCH

The Efficacy and Safety of First-Line Single-Inhaler Triple versus Dual Therapy in Controller-Naïve and Symptomatic Adults with Asthma: A Preliminary Retrospective Cohort Study

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Purpose: The efficacy and safety of first-line triple and dual therapy remain unclear because the stepwise strategy is a worldwide standard in controller-naïve asthma. A preliminary retrospective cohort study was conducted to investigate the efficacy and safety of first-line triple and dual therapy for managing controller-naïve and symptomatic adult patients with asthma.

Patients and Methods: Patients with asthma who received first-line single-inhaler triple therapy (SITT) or dual therapy (SIDT) for at least 8 weeks were selected between December 1, 2020, and May 31, 2021, in Fujiki Medical and Surgical Clinic, Miyazaki, Japan. Data on daytime and nighttime visual analog scale (VAS) scores, lung function tests, fractional exhaled nitrogen oxide (F_ENO), and adverse events were compared between SITT and SIDT pre- and post-treatment.

Results: The SITT significantly improved the nighttime, but not daytime, VAS scores better than the SIDT 2 weeks post-treatment ($P = 0.0026$), whereas SITT and SIDT significantly improved daytime and nighttime VAS scores after treatment compared to baseline. Both therapies also significantly improved lung functions and F_ENO post-treatment. The proportion of patients achieving complete control in the nighttime VAS scores after SITT was significantly higher than that four ($P = 0.0186$) and 8 weeks ($P = 0.0061$) after SIDT. Only patients with SITT experienced dry mouth.

Conclusion: Our study demonstrated that first-line SITT and SIDT were effective, and SITT improved disease control faster than SIDT in controller-naïve and symptomatic adult patients with asthma. The first-line SITT may contribute to faster and better control levels in symptomatic patients with asthma.

Keywords: adult, asthma, cohort study, corticosteroids, Japanese

Plain Language Summary

This preliminary retrospective cohort study aimed to investigate the efficacy and safety of the first-line triple therapy for controller-naïve and symptomatic adult patients with asthma and compare triple and dual therapies using a visual analog scale to assess the general conditions of patients with asthma in Japan. Our study demonstrated that the single-inhaler triple therapy improved disease control, especially nocturnal symptoms, faster than the single-inhaler dual therapy.

Introduction

The Global Initiative for Asthma (GINA) report recommends a stepwise strategy of pharmacological treatments for asthma.[1] A triple therapy (inhaled corticosteroid [ICS]/long-acting beta-2 agonist [LABA]/long-acting muscarinic antagonist [LAMA]) is effective for managing moderate-to-severe asthma.[2–6] However, triple therapy is recommended as a second-line treatment for patients with uncontrolled asthma using ICS/LABA dual therapy.[1] The GINA reports also

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recommend that ICS/LABA dual therapy be selected in patients with uncontrolled asthma using low-dose ICS monotherapy.[1] Therefore, first-line triple and dual therapies may not be used in patients with asthma. However, the strategies may be permitted as a first-line treatment in patients with asthma and chronic pulmonary obstructive disease (COPD) overlap and asthma with airflow obstructions.[7–10]

Patients with uncontrolled or severe asthma have been a social challenge worldwide[11–13] and in Japan.[14] In 2021, the Middle East and North Africa survey using the GINA criteria reported that the percentage of patients with partly controlled and uncontrolled asthma was 29.1% and 41.5%, respectively.[11] A 2009 US survey demonstrated that although 71% of the patients reported "completely controlled" or "well controlled" by themselves, the percentage of patients with asthma who made urgent care visits twice and emergency visits once yearly was 67% and 60%, respectively.[12] A global cross-sectional study in 2016 demonstrated that among 8111 patients, 18.0% and 38.5% had partly controlled and uncontrolled asthma, respectively.[13] A Japanese internet survey reported that based on the GINA criteria, 49.8% and 15.1% of the patients had partly controlled and uncontrolled asthma, respectively. Daytime and nighttime asthma symptoms were experienced by 51.5% and 44.9% of the patients, respectively.[14] A global study observed that under-treatments still occur in managing asthma worldwide.[15]

Questionnaires specializing in asthma help to grasp the health-related quality of life (HRQoL) and severity of asthmatic symptoms as assessment tools for patient-reported outcomes (PROs),[16–21] although a recognition gap of controlled levels between physicians and patients is well known in asthma.[12,14,22–28] Severe asthmatic symptoms influence asthma-related mortality.[29,30] Therefore, asthmatic symptoms should be relieved as immediately as possible. Early and intensive inhaled medicines may improve disease control and reduce mortality in asthma. The efficacy and safety of first-line triple therapy remain unclear, although previous studies have already reported the usefulness of first-line dual therapy in controller-naïve and symptomatic patients with asthma.[28,31–34] Therefore, we conducted a preliminary retrospective cohort study to investigate the efficacy and safety of the first-line triple therapy for controller-naïve and symptomatic adult patients with asthma and compare triple and dual therapies using a visual analog scale (VAS) to assess the general conditions of patients with asthma in Japan.

Materials and Methods

Study Protocol

A retrospective study was conducted in a single institute and primary care setting. Fujiki Medical and Surgical Clinic routinely required clinical information such as self-reported daytime and nighttime VAS and ACT scores as PROs, prescriptions, body mass index, smoking habits, comorbidities (Supplementary Table 1), blood eosinophil counts, serum total IgE levels, lung functions using spirometry, and fractional exhaled nitrogen oxide (F_ENO) before treatment for each patient with asthma. The clinic also determined daytime and nighttime VAS 2, 4, and 8 weeks after treatment, ACT scores 4 and 8 weeks after treatment, and lung function test results and F_ENO measurements 8 weeks after treatment. The clinic staff always asks each patient about adverse events and medication adherence at every visit during treatment. Each patient was taught the correct inhalation technique before treatment and 2, 4, and 8 weeks after treatment. The remaining counters or capsules for Ellipta®and Turbuhaler® or Breezhaler®, respectively, and the interview manner for pressurized metered dose inhalers (pMDI) were checked to assess adherence to controllers for asthma (Figure 1). We confirmed that all patients had good adherence with >80% administration during the assessment period. However, the measurements of airway reversibility were unavailable using inhaled short-acting bronchodilators in the clinic. All data were retrospectively collected from the medical records in the clinic.

Patients

Among all patients who visited the clinic, 308 with asthma were treated using single-inhaler triple therapy (SITT) or single-inhaler dual therapy (SIDT) for at least 8 weeks between December 1, 2020 and May 31, 2021 (Figure 2). Asthma was diagnosed by the physician based on the GINA report.[1] All the patients had experienced fluctuating chronic respiratory symptoms of cough, sputum, and wheezing before clinic visits. The self-management of short-acting beta-2 agonists was used against milder exacerbations, as none were permitted single-maintenance and reliever therapy. None

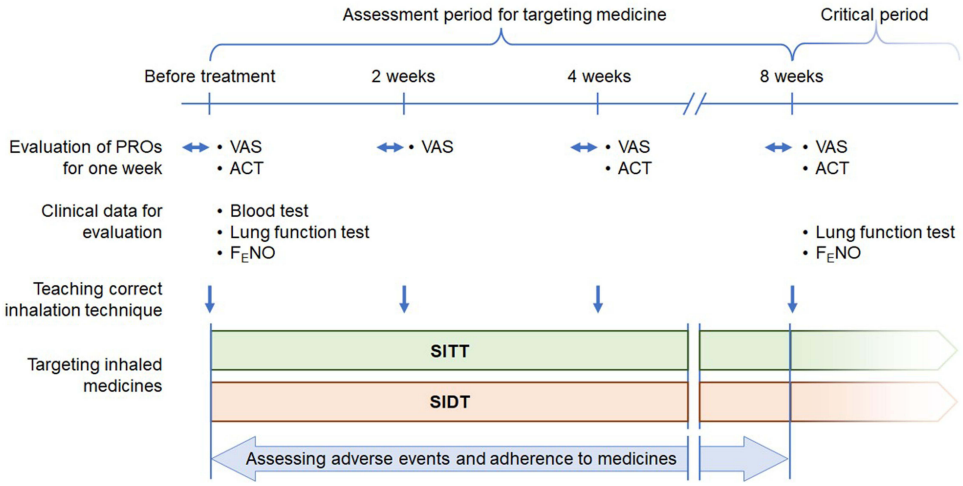

Figure 1 Study design.
Abbreviations: ACT, asthma control test; F_ENO, fractional exhaled nitrogen oxide; PROs, patient-reported outcomes; SIDT, single-inhaler dual therapy; SITT, single-inhaler triple therapy; VAS, visual analog scale.

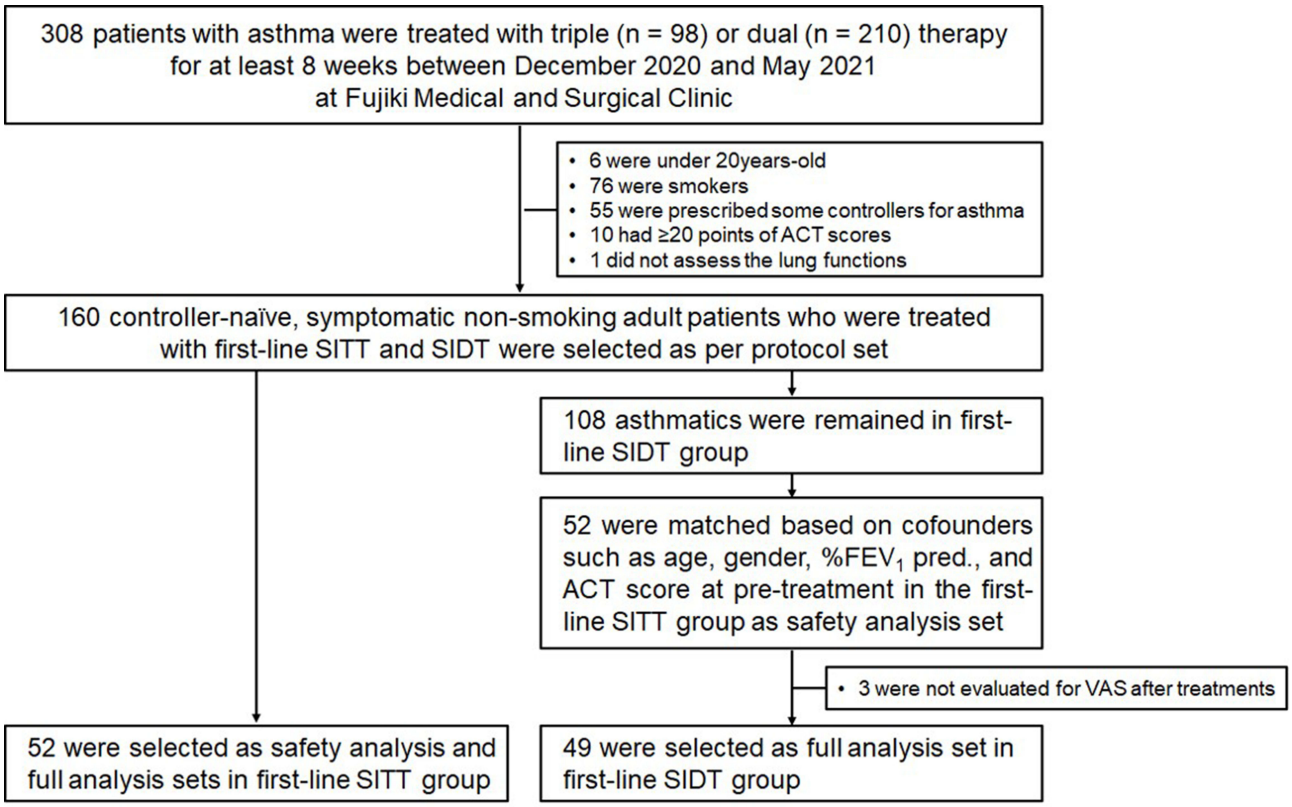

Figure 2 Patient selection.
Abbreviations: SIDT, single-inhaler dual therapy; SITT, single-inhaler triple therapy; VAS, visual analog scale.

had moderate-to-severe exacerbations that required systemic corticosteroids and hospitalization for at least a last year. We selected the controller-naïve (no prescriptions for controllers, such as ICS, LABA, LAMA, leukotriene antagonists, and biologics for asthma treatments for at least 6 months), symptomatic (ACT <20 points), non-smoking, adult (aged ≥20 years) patients before SITT and SIDT. Patients <20 years of age (n = 6), current and former smokers (n = 76), those prescribed some controllers for asthma (n = 55), those with ≥20 ACT points (n = 10), and those whose lung functions

were not assessed pre-treatment (n = 1) were excluded. None received multi-device inhaler therapy. There were 52 patients with asthma on first-line SITT (patients with SITT as the final analysis cohort) and 108 on first-line SIDT (Supplementary Table 2). To ensure a balanced comparison between patients treated using SITT and SIDT, 52 patients with asthma on SIDT were randomly selected using 1:1 matching with those on SITT considering potentially confounding factors of age, gender, percent predicted value of forced expiratory volume in 1 second (%FEV_1 predicted), and total ACT scores at pre-treatment.[16,17] However, three were excluded without VAS assessment at 2, 4, or 8 weeks after treatment. Finally, 49 patients with SIDT were adopted as a control for patients with SITT (Figure 2).

Data Collection

PROs

The self-reporting ACT[16,17,35] and VAS[23–28] assessments were required before F_ENO and lung function measurements. The modified ACT and VAS assessed asthma symptoms the week before the evaluation period (Figure 1). Two types of modified VAS exist, daytime (6 am–6 pm) and nighttime VAS (6 pm–6 am), which were used based on the Japanese version of the VAS used in a previous study.[24,28] In the VAS, the scales ranged from not bothersome at all (0 cm as a good condition) to extremely bothersome (10 cm as a bad condition). After reporting daytime and nighttime VAS, each patient continuously underwent the Japanese version of the ACT for adult patients with asthma.[35] The minimal clinically important difference (MCID) between pre- and post-treatment was defined as a 3-point change in ACT scores and −4.6-cm change for daytime and nighttime VAS based on previous studies.[28,35] The complete control level was at an ACT score of 25 points or when the daytime and nighttime VAS reached 0 cm post-treatment.

Measurement of F_ENO

The morning F_ENO was measured twice daily at every visit before spirometry using an online electrochemical NO analyzer (NIOX VERO®, Circassia AB, Sweden). The mean value was used for the analysis.[36]

Lung Function Tests

Spirometry (Chestgraph Jr HI-101, CHEST, Tokyo, Japan) was repeated twice. We adopted the best FEV_1 and forced vital capacity (FVC) values per a Taskforce recommendation.[37] The %FEV_1 predicted and percent predicted value of FVC (%FVC predicted) were estimated using a formula for Japanese individuals.[38] Spirometric-restrictive and obstructive ventilatory patterns were defined as %FVC predicted <80% with FEV_1/FVC ratio ≥0.7 and FEV_1/FVC ratio <0.7, respectively.[39]

Ethical Considerations

The study was conducted following the Good Clinical Practice guidelines in accordance with the Helsinki Declaration and was approved by the local ethics board of Kurume University, Japan (No. 21–155, September 30, 2021). The study protocol was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. 000045636) on October 2, 2021. Patients who visited Fujiki Medical and Surgical Clinic (Miyazaki, Japan) were allowed to opt out between September 30, 2021, and March 31, 2022.

Statistical Analysis

All data were expressed as the number (% of total) of patients and mean ± standard deviation (SD). Data were compared using Fisher's exact test, Welch's *t*-test, and Mann–Whitney's *U*-test. Changes in data from the baseline were compared using the Student's *t*-test and one-way analysis of variance test. The selected ICS dose equivalences between SITT and SIDT were calculated using the glucocorticoid receptor-binding affinity of dexamethasone in accordance with a previous study.[40] Statistical significance was set at $P < 0.05$. We used the JMP version 15 for Windows (SAS Institute, Cary, NC, USA) for data analyses and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) for control matching.

Results

Characteristics of Patients on SITT and SIDT Pre-Treatment

Table 1 presents the characteristics of patients on SITT and SIDT, before treatment. In first-line SITT and SIDT regimens, no difference was observed in the number (% of total) of patients with high-dose ICS between SITT (n = 15 [28.8%]) and SIDT (n = 20 [40.8%]) ($P = 0.2182$). All patients on SITT and 25 [51.0%] on SIDT inhaled once daily ($P < 0.0001$), whereas the remaining 24 [49.0%] inhaled SIDT twice daily. In the analysis of the ICS dose equivalence using the glucocorticoid receptor-binding affinity of dexamethasone (Supplementary Table 3),[40] the mean (SD) ICS dose in SITT (3323 [1422] μ/day) was significantly lower than that in the SIDT group (6536 [1812]) ($P < 0.0001$).

Comparison of Changes in ACT Scores and Daytime and Nighttime VAS Between SITT and SIDT Post-Treatment

Figure 3 illustrates that SITT and SIDT significantly improve ACT scores 4 and 8 weeks post-treatment and daytime and nighttime VAS 2, 4, and 8 weeks post-treatment compared to baseline. The SITT significantly improved the nighttime VAS, but not daytime, better than the SIDT 2 weeks after treatment ($P = 0.0026$). Supplementary Figure 1 compares the mean PRO values between SITT and SIDT at each visit. None had unscheduled or emergency visits or moderate-to-

Table 1 Characteristics of Patients with Asthma Undergoing SITT and SIDT

Characteristics	SITT, n = 52	SIDT, n = 49	*P*-value
Age, years, mean ± SD	48.8 ± 16.9	50.0 ± 16.2	0.7
Female, n (%)	36 (69.2)	36 (73.5)	0.7
Body mass index, kg/m^2, mean ± SD	23.9 ± 3.8	22.8 ± 3.7	0.2
Any other allergic comorbidities, n (%)	23 (44.2)	16 (32.7)	0.3
Allergic rhinitis	22 (42.3)	16 (32.7)	0.4
Chronic sinusitis with nasal polyps	2 (3.9)	1 (2.0)	1.0
Atopic dermatitis	0 (0)	1 (2.0)	0.5
PROs, mean ± SD			
ACT score, points	13.6 ± 3.3	13.5 ± 3.0	0.9
VAS, cm			
Daytime	7.1 ± 2.4	7.5 ± 1.7	0.3
Nighttime	7.4 ± 2.1	7.7 ± 1.9	0.5
Lung functions, mean ± SD			
FVC, L	2.85 ± 0.70	2.80 ± 0.77	0.9
%FVC predicted, %	95.8 ± 15.3	96.4 ± 19.3	0.9
FEV_1, L	2.37 ± 0.67	2.25 ± 0.68	0.4
% FEV_1 predicted, %	92.5 ± 18.7	92.1 ± 22.6	0.9
FEV_1/FVC ratio	0.83 ± 0.10	0.80 ± 0.09	0.1
Spirometric ventilatory pattern, n (%)			
Obstructive ventilatory pattern	4 (7.7)	7 (14.3)	0.3
Restrictive ventilatory pattern	7 (13.5)	3 (6.1)	0.3
Biomarkers, mean ± SD			
Blood eosinophil count, cells/μL	266 ± 246	230 ± 152	0.4
Serum total IgE, U/mL	177 ± 242	144 ± 242	0.5
F_ENO, ppb	34.3 ± 28.1	42.9 ± 35.5	0.2
Other concomitant medicines, n (%)			
Leukotriene antagonist	18 (34.6)	22 (44.9)	0.3
Other allergic or antihistamine drugs	17 (32.7)	10 (20.4)	0.2

Notes: Data are expressed as mean ± standard deviation and number (%) of patients. Other concomitant medicines were used before and after SITT and SIDT. However, no patient was administered slow-release theophylline, regular oral prednisolone, and biologics.
Abbreviations: ACT; asthma control test, F_ENO; fractional exhaled nitric oxide, FEV_1; forced expiratory volume in one second, FVC; forced vital capacity, %FEV_1 predicted; percent predicted value of FEV_1, %FVC predicted; percent predicted value of FVC, PROs; patient-reported outcomes, SD; standard deviation, SIDT; single-inhaler dual therapy, SITT; single-inhaler triple therapy, VAS; visual analog scale.

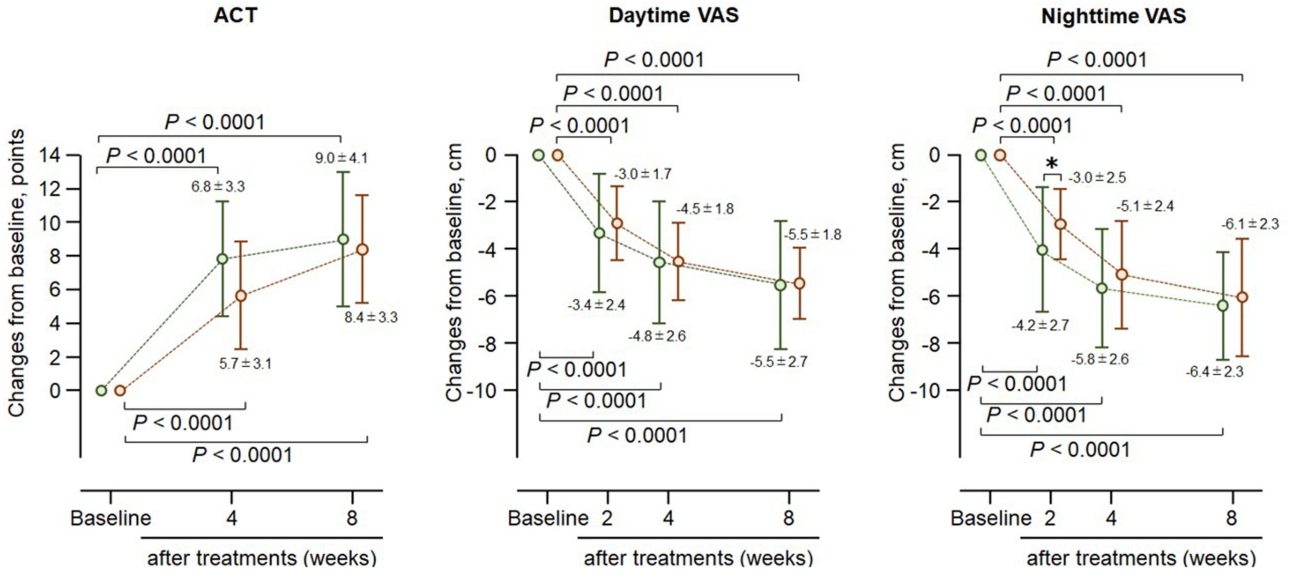

Figure 3 Comparison of ACT changes and day and nighttime VAS scores post-treatment between SITT and SIDT.
Notes: Changes (%) from baseline were expressed as mean ± SD in the ACT and day and nighttime VAS. *P = 0.0026 comparing SITT and SIDT 2 weeks post-treatment.
Abbreviations: ACT, asthma control test; SD, standard deviation; SIDT, single-inhaler dual therapy; SITT, single-inhaler triple therapy; VAS, visual analog scale.

severe exacerbations requiring systemic corticosteroids and hospitalization and there were no deaths during the assessment period.

Comparison of the Proportion of Patients Reaching the MCID and Complete Control Levels Between SITT and SIDT Post-Treatment

Figure 4 illustrates the proportion of patients achieving the MCID and complete control levels post-treatment. The proportions of patients achieving the MCID (odds ratio [OR] of SITT related to SIDT [95% confidential index]) 2 weeks after SITT were significantly higher than those for the daytime (OR 3.18 [1.19 to 9.49], P = 0.0218) and nighttime VAS scores (OR 2.99 [1.30 to 6.90], P = 0.0142) 2 weeks after SIDT (Figure 4A). In addition, the proportion of patients reaching complete control levels in the ACT scores 8 weeks after SITT was significantly higher than those after SIDT (OR 4.60 [1.21 to 17.47], P = 0.0237), whereas those for the nighttime VAS scores 4 and 8 weeks after SITT were significantly higher than those 4 (OR 4.14 [1.26 to 13.65], P = 0.0186) and 8 weeks (OR 3.61 [1.49 to 8.73], P = 0.0061) after SIDT (Figure 4B).

Efficacy of SITT and SIDT for Lung Functions and F_ENO

Table 2 presents lung function and F_ENO changes 8 weeks post-treatment. No changes were observed in lung functions and F_ENO 8 weeks post-treatment in SITT and SIDT.

Safety of First-Line SITT and SIDT

Table 3 presents adverse events in SITT and SIDT. No difference was observed in the proportion of patients with adverse events between SITT (28.9%) and SIDT (24.5%). The most common adverse event was dysphonia, followed by transient coughing after administration. Comparing SITT and SIDT, five patients undergoing SITT, but not SIDT, experienced dry mouth. Considering the device type, the number (% of users) of patients with dysphonia and transient coughing after administration was 8 (14.3%) and 4 (7.1%) with Ellipta®, 2 (15.4%) and 1 (7.7%) with Turbuhaler®, 1 (5.0%) and 1 (5.0%) with Breezhaler®, and 1 (8.3%) and 0 (0%) with the pMDI. However, none of the patients discontinued treatment due to adverse events, experienced severe adverse events, or died in SITT and SIDT during the 8-week treatment period.

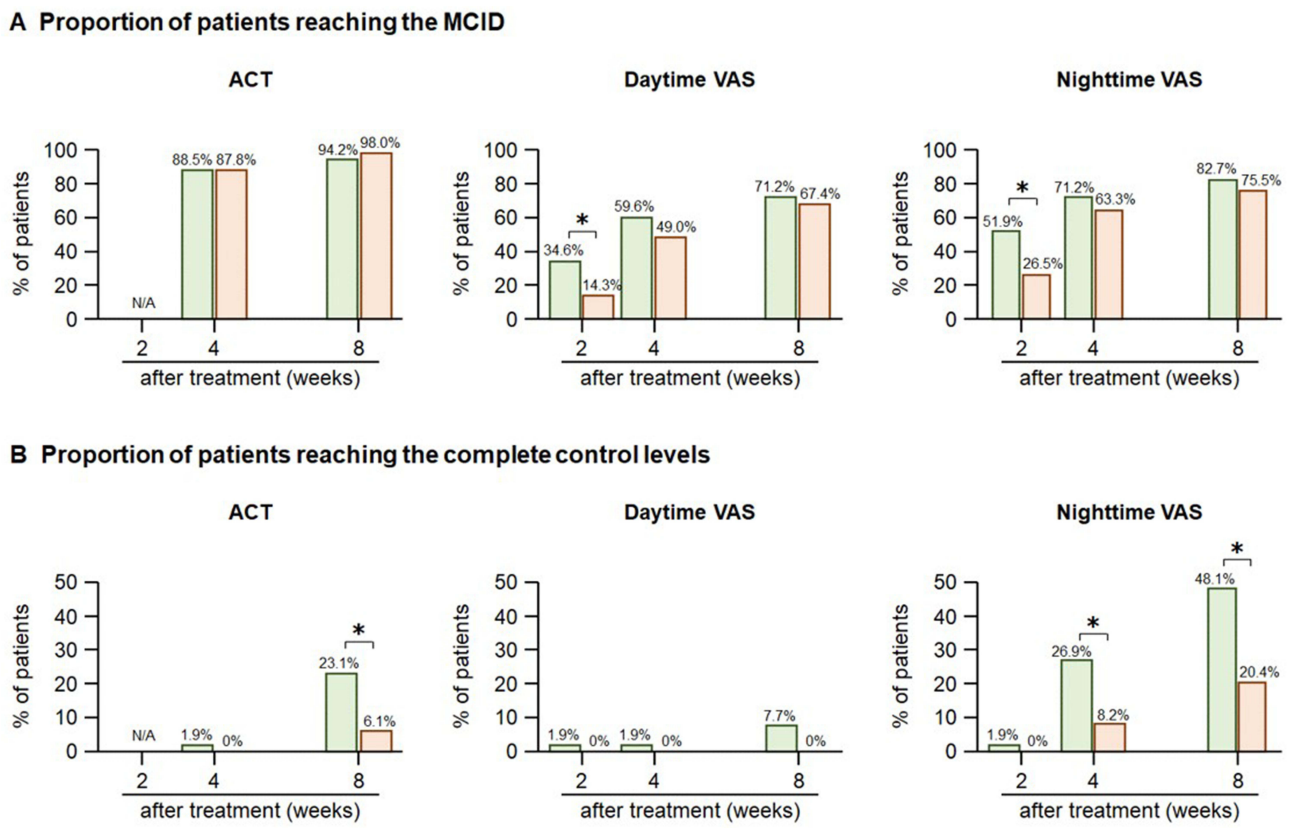

Figure 4 Comparison of the proportion of patients achieving the MCID and complete control between SITT and SIDT post-treatment.
Notes: Data were expressed as percentages of patients in SITT (green bars) and SIDT (red bars). (**A**) proportion of patients reaching the MCID, (**B**) proportion of patients achieving complete control. SITT for green bars, SIDT for red bars. *$P < 0.05$ between SITT and SIDT in each visit.
Abbreviations: ACT, asthma control test; N/A, not available; SIDT, single-inhaler dual therapy; SITT, single-inhaler triple therapy; VAS, visual analog scale.

Discussion

Our preliminary retrospective cohort study demonstrated that first-line SITT and SIDT safely improved the asthma control levels in controller-naïve and symptomatic adult patients with asthma. Our study also revealed that SITT significantly improved the control levels faster than SITD in nighttime VAS assessment 2 weeks post-treatment. In addition, a higher proportion of patients with SITT achieved the MCID of daytime VAS 4 weeks and of nighttime VAS 2 weeks post-treatment than that with SIDT. The SITT helped achieve complete control levels as per the ACT in 23.1% of the patients in 8 weeks and as per the nighttime VAS in 26.9% of the patients in 4 weeks and 48.1% in 8 weeks post-treatment. However, SITT and SIDT significantly improved lung functions and F_ENO 8 weeks post-treatment, although there was no significant difference in lung functions and F_ENO between the treatment groups. Furthermore, our results may suggest that some patients are undertreated

Table 2 Changes in Lung Functions and F_ENO Between SITT and SIDT 8 Weeks After Treatment

Evaluation Post-Treatment	SITT, n = 52	SIDT, n = 49	*P*-value
FVC, mL	162 ± 317	159 ± 318	0.9607
%FVC predicted, %	5.9 ± 11.1	5.7 ± 10.9	0.9263
FEV_1, mL	195 ± 298	254 ± 328	0.3473
$\%FEV_1$ predicted, %	8.5 ± 11.2	10.0 ± 11.9	0.5294
F_ENO, ppb	−8.2 ± 17.8	−14.0 ± 24.9	0.1808

Note: No patient had malignancies or chronic kidney diseases.
Abbreviations: ACT; asthma control test, SIDT; single-inhaler dual therapy, SITT; single-inhaler triple therapy.

Table 3 Adverse Events Using SITT and SIDT

Adverse Events	SITT, n = 52	SIDT, n = 49	*P*-value
Any adverse events	15 (28.9)	12 (24.5)	0.7
Serious adverse events	0 (0)	0 (0)	1.0
Adverse events leading to discontinuation	0 (0)	0 (0)	1.0
Adverse events leading to death	0 (0)	0 (0)	1.0
Dysphonia	5 (9.6)	7 (14.3)	0.5
Transient coughing after administration	4 (7.7)	2 (4.1)	0.7
Dry mouth	5 (9.6)	0 (0)	0.1
Respiratory tract infections	2 (3.9)	1 (2.0)	1.0
Dyspepsia	2 (3.9)	0 (0)	0.5
Oral candidiasis	1 (1.9)	0 (0)	1.0
Diarrhea	0 (0)	1 (2.0)	0.5
Leg muscle cramps	0 (0)	1 (2.0)	0.5

Note: No patients had episodes of pneumonia.
Abbreviations: SIDT; single-inhaler dual therapy, SITT; single-inhaler triple therapy.

using first-line SIDT. In terms of treatment safety, none discontinued due to adverse events, had severe adverse events, or died while undergoing SITT and SIDT during the 8-week treatment period.

The self-reporting ACT and daytime and nighttime VAS may have some discrepancies in the disease control levels in each controller-naïve and symptomatic patient with asthma.[28] Comparing daytime and nighttime VAS among individuals, nighttime VAS was worse than daytime VAS. However, nighttime VAS improved faster than daytime VAS.[28] In our study, the proportion of patients that achieved the MCID and complete control assessed using the ACT differed from that assessed using the daytime and nighttime VAS as a discrepancy among PROs (Figure 4). Nighttime asthma symptoms and sleep disorders are common in patients with asthma and can be detrimental to their HRQoL.[41,42] The frequency of nighttime asthma symptoms observed in patients with asthma was consistent with that in a previous study, 37–47%.[43,44] Nocturnal symptoms cause poorer HRQoL than daytime symptoms in patients with asthma. A previous study demonstrated that individuals with asthma and COPD hoped that their nocturnal asthma symptoms did not disturb their sleep.[45] The optimal management may reduce nocturnal symptoms faster than daytime symptoms and improve sleep quality faster. The different general assessments of daytime and nighttime conditions may be significant using the daytime and nighttime VAS in patients with uncontrolled asthma.[28] Thus, early relief of nocturnal symptoms may improve general conditions faster than daytime symptom relief.[28] Our study showed that SITT efficacy appeared faster than SIDT efficacy for nighttime VAS and ACT scores but not for daytime VAS. A Japanese large-scale survey demonstrated that 76.4% of the patients with asthma had treatment expectations of rapid onset of action.[14]

All previous large-scale studies of single- or multiple-inhaler triple therapy enrolled patients with uncontrolled asthma despite treatment with high or medium ICS doses or LABA as prescriptions.[3,5,46,47] The efficacy and safety of first-line triple therapy have little evidence. However, second- or third-line triple therapy is widely approved in asthma.[3,5,46,47] Adding LAMA to ICS/LABA minimally reduced exacerbations and improved disease control levels. However, triple therapy improved lung functions more than ICS/LABA dual therapy in patients with moderate-to-severe asthma.[1,3,5,46,47] In our total study population, the frequency of patients with the obstructive ventilatory pattern was 7.7% in SITT and 14.3% in SIDT. However, first-line triple therapy should be selected for patients with asthma experiencing airflow limitation, such as ACO.[7–10] Our study did not show that SITT provided a more significant improvement in lung function than SIDT 8 weeks after treatment. In addition, the reducing effects on F_ENO after treatment were similar between SITT and SIDT. However, SITT led to faster asthma control improvement than SIDT and a higher proportion of patients who achieved the MICD and complete control in terms of PROs than SIDT. Adding LAMA to ICS/LABA therapy may attenuate mucus hypersecretion and cough, but its effect is not limited to bronchodilation and anti-inflammation.[3,5,46–49] Comparing high (doubling doses of medium-dose) and medium doses, previous studies[3,5] demonstrated that high-dose SITT and SIDT had more attenuated effects on moderate-to-severe exacerbations than medium-dose ones. Our study uncovered a bias in the ICS dose between SITT and SIDT, with the mean ICS dose in SITT being about half the dose in

SIDT. Nevertheless, the SITT improved asthma control faster than SITT. However, none had moderate-to-severe exacerbation pre- and post-treatment among our patients.

Regarding the safety of first-line SITT and SIDT, both therapies did not lead to any severe adverse events, and there was no adverse event leading to SITT and SIDT discontinuation during the assessment period. Therefore, the safety of both therapies was guaranteed. The most common adverse event was dysphonia, in 9.6% of the patients on SITT and in 14.3% on SIDT. The PrimoTinA-asthma study[46] demonstrated that 1.7–1.8% of the patients on ICS/LABA and 2.1–2.3% of the patients with LAMA added to ICS/LABA had dysphonia, whereas approximately 2% of the patients had dysphonia in the TRIMARAN and TRIGGER study.[47] The CAPTAIN[3] and IRIDIUM[5] studies reported no patients with dysphonia using single-inhaler devices. The next common adverse event was transient coughing after administration. Dysphonia and coughing are unavoidable biological reactions to inhaled medicines. Dysphonia may develop due to the inhaled medicine, but not due to differences in compounds, devices, or particle sizes of drugs. Dry mouth should be an adverse event of concern when adding LAMA.

Our study had several study limitations. First, the sample size was small compared to that in previous comparative studies between triple and dual therapies.[3,5,46,47] Second, our study was conducted by one physician and at one institution. The physician assessed all baseline information and clinical data before choosing controllers and continuously selected SITT or SIDT for each patient. The patient proportions may have biases between the SITT and SIDT. However, the proportion of patients on SIDT was randomly selected using cofounders. Furthermore, the physician's bias may affect our results. In fact, the daily doses of ICS differed between treatment groups. Nonetheless, the potency of corticosteroids was limited to comparison using only the glucocorticoid receptor-binding affinity.[40] The bias may be because the physician was more confident adding lower ICS doses as required for better control to dual bronchodilators. In contrast, the physician might have been uneasy about adding higher doses of ICS to a mono-bronchodilator. Third, this was a retrospective study. The timing of spirometry and F_ENO measurement was inconsistent pre- and post-treatment. The data were not always through values. Fourth, the eight-week assessment period was short for our study. We did not observe any moderate-to-severe exacerbations. In addition, mild exacerbations requiring short-acting bronchodilators were not assessed because our study did not acquire the self-reporting daily journal from each patient. A multi-institution, long-term, prospective study is therefore needed in the future.

Conclusions

Our retrospective study demonstrated that the SITT improved disease control, especially nocturnal symptoms, faster than the SIDT. However, first-line SITT and SIDT safely increased lung functions and decreased F_ENO in controller-naïve and symptomatic adult Japanese patients with asthma. Adding LAMA to ICS/LABA may provide a more rapid response to complete control than doubling ICS doses with LABA. However, dry mouth should be an adverse event of concern, more in SITT than in SIDT. Furthermore, the characteristics of patients that determine the treatment option—SITT or SIDT—should be first determined; however, the step-down strategy remains unclear.

Abbreviations

ACT, asthma control test; COPD, chronic pulmonary obstructive disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; F_ENO, fractional exhaled nitrogen oxide; GINA, Global Initiative for Asthma; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; OR, odds ratio; $\%FEV_1$ predicted, percent predicted value of FEV_1; %FVC predicted, percent predicted value of FVC; pMDI, pressurized metered dose inhaler; UMIN, University Hospital Medical Information Network; PROs, patient-reported outcomes; SIDT, single-inhaler dual therapy; SITT, single-inhaler triple therapy; SD, standard deviation; VAS, visual analog scale.

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References

1. Global Initiative for Asthma. The global strategy for asthma management and prevention; 2021. Available from: https://ginasthma.org/. Accessed March 9, 2022.
2. Kim LHY, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs dual inhaler therapy and asthma outcomes in moderate to severe asthma: a systematic review and meta-analysis. *JAMA*. 2021;325(24):2466–2479. doi:10.1001/jama.2021.7872
3. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, Phase 3A trial. *Lancet Respir Med*. 2021;9(1):69–84. doi:10.1016/S2213-2600(20)30389-1
4. Nakamura Y, Hozawa S, Sagara H, et al. Efficacy and safety of once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol in Japanese patients with inadequately controlled asthma: the CAPTAIN study. *Curr Med Res Opin*. 2021;37(9):1657–1665. doi:10.1080/03007995.2021.1944849
5. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med*. 2020;8(10):1000–1012. doi:10.1016/S2213-2600(20)30190-9
6. Sagara H, Barbier N, Ishii T, et al. Efficacy of one time per day, single-inhaler indacaterol/glycopyrronium/mometasone in patients with inadequately controlled asthma: post hoc analysis of IRIDIUM study in Asian population. *BMJ Open Respir Res*. 2021;8(1):e000856. doi:10.1136/bmjresp-2020-000856
7. Padrão E, Araújo D, Todo Bom A, et al. Asthma-COPD overlap: a Portuguese survey. *Pulmonology*. 2018:S2173–5115. doi:10.1016/j.rppnen.2017.11.009
8. Park SY, Kim S, Kim JH, et al. A randomized, noninferiority trial comparing ICS + LABA with ICS + LABA + LAMA in Asthma-COPD overlap (ACO) treatment: the ACO Treatment With Optimal Medications (ATOMIC) study. *J Allergy Clin Immunol Pract*. 2021;9(3):1304–1311. doi:10.1016/j.jaip.2020.09.066
9. Ishiura Y, Fujimura M, Ohkura N, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate improves inspiratory capacity in patients with asthma-chronic obstructive pulmonary disease overlap. *Int J Chron Obstruct Pulmon Dis*. 2020;15:269–277. doi:10.2147/COPD.S231004
10. Yanagisawa S, Ichinose M. Definition and diagnosis of asthma-COPD overlap (ACO). *Allergol Int*. 2018;67(2):172–178. doi:10.1016/j.alit.2018.01.002
11. Bassam M, Behbehani N, Farouk H, et al. Adherence to medication among adult asthma patients in the Middle East and North Africa: results from the ESMAA study. *Respir Med*. 2021;176:106244. doi:10.1016/j.rmed.2020.106244
12. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 asthma insight and management survey. *Allergy Asthma Proc*. 2012;33(1):54–64. doi:10.2500/aap.2011.32.3518
13. Braido F, Brusselle G, Guastalla D, et al. Determinants and impact of suboptimal asthma control in Europe: the international cross-sectional and longitudinal assessment on asthma control (LIAISON) study. *Respir Res*. 2016;17(1):51. doi:10.1186/s12931-016-0374-z
14. Adachi M, Hozawa S, Nishikawa M, Yoshida A, Jinnai T, Tamura G. Asthma control and quality of life in a real-life setting: a cross-sectional study of adult asthma patients in Japan (ACQUIRE-2). *J Asthma*. 2019;56(9):1016–1025. doi:10.1080/02770903.2018.1514628
15. Reddel HK, Vestbo J, Agustí A, et al. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. *Eur Respir J*. 2021;58(3):2003927. doi:10.1183/13993003.03927-2020
16. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65. doi:10.1016/j.jaci.2003.09.008
17. Schatz M, Sorkness CA, Li JT, et al. Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. 2006;117:549–556. doi:10.1016/j.jaci.2006.01.011
18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–907. doi:10.1034/j.1399-3003.1999.14d29.x
19. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553–558. doi:10.1016/j.rmed.2004.10.008
20. Jia CE, Zhang HP, Lv Y, et al. The asthma control test and asthma control questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2013;131(3):695–703. doi:10.1016/j.jaci.2012.08.023
21. Szentes BL, Schultz K, Nowak D, Schuler M, Schwarzkopf L. How does the EQ-5D-5L perform in asthma patients compared with an asthma-specific quality of life questionnaire. *BMC Pulm Med*. 2020;20(1):168. doi:10.1186/s12890-020-01205-8
22. Matsunaga K, Hamada K, Oishi K, Yano M, Yamaji Y, Hirano T. Factors associated with physician-patient discordance in the perception of asthma control. *J Allergy Clin Immunol Pract*. 2019;7(8):2634–2641. doi:10.1016/j.jaip.2019.04.046
23. Ciprandi G, Schiavetti I, Sorbello V, Ricciardolo FL. Perception of asthma symptoms as assessed on the visual analog scale in subjects with asthma: a real-life study. *Respir Care*. 2016;61(1):23–29. doi:10.4187/respcare.04171

24. Ohta K, Jean Bousquet P, Akiyama K, et al. Visual analog scale as a predictor of GINA-defined asthma control. The SACRA study in Japan. *J Asthma*. 2013;50(5):514–521. doi:10.3109/02770903.2013.786726
25. Flood EM, De Cock E, Mörk AC, Revicki DA. Evaluating preference weights for the Asthma Symptom Utility Index (ASUI) across countries. *Health Qual Life Outcomes*. 2006;4:51. doi:10.1186/1477-7525-4-51
26. Laforest L, El Hasnaoui A, Pribil C, Ritleng C, Schwalm MS, Van Ganse E. Asthma patients' perception of their ability to influence disease control and management. *Ann Allergy Asthma Immunol*. 2009;102(5):378–384. doi:10.1016/S1081-1206(10)60508-X
27. Laforest L, El Hasnaoui A, Pribil C, et al. Asthma patients' self-reported behaviours toward inhaled corticosteroids. *Respir Med*. 2009;103 (9):1366–1375. doi:10.1016/j.rmed.2009.03.010
28. Fujiki R, Kawayama T, Furukawa K, Kinoshita T, Matsunaga K, Hoshino T. Daytime and nighttime visual analog scales may be useful in assessing asthma control levels before and after treatment. *J Asthma Allergy*. 2022;15:1549–1559. doi:10.2147/JAA.S381985
29. Bourdin A, Fabry-Vendrand C, Ostinelli J, et al. The burden of severe asthma in France: a case-control study using a medical claims database. *J Allergy Clin Immunol Pract*. 2019;7(5):1477–1487. doi:10.1016/j.jaip.2018.12.029
30. Omachi TA, Iribarren C, Sarkar U, et al. Risk factors for death in adults with severe asthma. *Ann Allergy Asthma Immunol*. 2008;101(2):130–136. doi:10.1016/S1081-1206(10)60200-1
31. Seale JP, Jenkins C, Wood-Baker R, et al. Benefits of fixed-dose combination therapy with inhaled corticosteroids and long-acting bronchodilators as initial maintenance therapy in the management of asthma. *Respirology*. 2009;14(2):224–229. doi:10.1111/j.1440-1843.2008.01440.x
32. Parimi M, Svedsater H, Ann Q, et al. Persistence and adherence to ICS/LABA drugs in UK patients with asthma: a retrospective new-user cohort study. *Adv Ther*. 2020;37(6):2916–2931. doi:10.1007/s12325-020-01344-8
33. Buhl R, Heaney LG, Loefroth E, et al. One-year follow up of asthmatic patients newly initiated on treatment with medium- or high-dose inhaled corticosteroid-long-acting β2-agonist in UK primary care settings. *Respir Med*. 2020;162:105859. doi:10.1016/j.rmed.2019.105859
34. Lin J, Fu X, Jiang P, et al. INITIAL - An observational study of disease severity in newly diagnosed asthma patients and initial response following 12 weeks' treatment. *Sci Rep*. 2019;9(1):1254. doi:10.1038/s41598-018-36611-w
35. Hasegawa T, Koya T, Sakagami T, et al. The Asthma Control Test, Japanese version (ACT-J) as a predictor of Global Initiative for Asthma (GINA) guideline-defined asthma control: analysis of a questionnaire-based survey. *Allergol Int*. 2013;62(3):323–330. doi:10.2332/allergolint.13-OA-0535
36. Exhaled NO. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912–930. doi:10.1164/rccm.200406-710ST
37. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805
38. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig*. 2014;52(4):242–250. doi:10.1016/j.resinv.2014.03.003
39. Soriano JB, Miravitlles M, García-Río F, et al. Spirometrically-defined restrictive ventilatory defect: population variability and individual determinants. *Prim Care Respir J*. 2012;21(2):187–193. doi:10.4104/pcrj.2012.00027
40. Daley-Yates PT. Inhaled corticosteroids: potency, dose equivalence and therapeutic index. *Br J Clin Pharmacol*. 2015;80(3):372–380. doi:10.1111/bcp.12637
41. Arif AA, Rohrer JE, Delclos GL. A population-based study of asthma, quality of life, and occupation among elderly Hispanic and non-Hispanic whites: a cross-sectional investigation. *BMC Public Health*. 2005;5:1. doi:10.1186/1471-2458-5-97
42. Luyster FS, Teodorescu M, Bleecker E, et al. Sleep quality and asthma control and quality of life in non-severe and severe asthma. *Sleep Breath*. 2012;16(4):1129–1137. doi:10.1007/s11325-011-0616-8
43. Fletcher M, Hiles D. Continuing discrepancy between patient perception of asthma control and real-world symptoms: a quantitative online survey of 1083 adults with asthma from the UK. *Prim Care Respir J*. 2013;22(4):431–438. doi:10.4104/pcrj.2013.00091
44. Maspero JF, Jardim JR, Aranda A, et al. Insights, attitudes, and perceptions about asthma and its treatment: findings from a multinational survey of patients from Latin America. *World Allergy Organ J*. 2013;6(1):19. doi:10.1186/1939-4551-6-19
45. Svedsater H, Roberts J, Patel C, Macey J, Hilton E, Bradshaw L. Life impact and treatment preferences of individuals with asthma and chronic obstructive pulmonary disease: results from qualitative interviews and focus groups. *Adv Ther*. 2017;34(6):1466–1481. doi:10.1007/s12325-017-0557-0
46. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367 (13):1198–1207. doi:10.1056/NEJMoa1208606
47. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet*. 2019;394(10210):1737–1749. doi:10.1016/S0140-6736(19)32215-9
48. Calzetta L, Ritondo BL, Zappa MC, et al. The impact of long-acting muscarinic antagonists on mucus hypersecretion and cough in chronic obstructive pulmonary disease: a systematic review. *Eur Respir Rev*. 2022;31(164):210196. doi:10.1183/16000617.0196-2021
49. Cazzola M, Ora J, Rogliani P, Matera MG. Role of muscarinic antagonists in asthma therapy. *Expert Rev Respir Med*. 2017;11(3):239–253. doi:10.1080/17476348.2017.1289844