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Research Article

Practical Evaluation of Triple Therapy Efficacy and Biomarkers in 200 Elderly Patients with Real-World Bronchial Asthma and ACO

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Abstract

Background: In clinical trials for bronchial asthma and ACO, triple therapy (a combination of Inhaled Corticosteroids [ICS] + Long-Acting Beta-Agonists [LABA] + Long-Acting Anticholinergics [LAMA]) is the current treatment. It has been reported to be more effective in improving respiratory function and reducing exacerbations than conventional methods. However, there are no reports verifying the effects, side effects, and efficacy in actual clinical settings.

Objective: This study aimed to investigate efficacy and biomarkers in elderly asthma and ACO patients treated with triple therapy.

Methods: This retrospective chart study included 201 patients from a single-center real-life geriatric population with bronchial asthma and Asthma-COPD Overlap (ACO) treated with ICS and LABA.

Results: Triple therapy is more effective than existing therapies in improving Asthma Control Test (ACT) results, Forced Expiratory Volume in one second (FEV1), and rates of asthma and ACO exacerbations. Our study provides evidence supporting the efficacy and safety of triple therapy in real-world geriatric settings, with no side effects that preclude its use. The reason for the good effect is that LAMA acts both as a tracheal stabilizer and a bronchodilator in patients with bronchial asthma, and because pulmonary acetylcholine in asthmatic patients may be elevated. It is possible.

Conclusion: In the real world, triple therapy should be actively used when symptoms such as high biomarker values, low FEV1 values, and a high frequency of exacerbations are observed.

Keywords: Elderly Patients; Bronchial Asthma; Triple Therapy; Long-Acting Anticholinergic Agents; Asthma-COPD Overlap

Abbreviations

ACO: Asthma-COPD Overlap; ACT: Asthma Control Test; ATS: American Thoracic Society; COPD: Chronic Obstructive Pulmonary Disease; FF+UME+VI: Fluticasone Furoate + Umeclidinium Bromide + Vilanterol Trifen; FVC: Forced Expiratory Volume in 1 s (FEV1)/ forced vital capacity; ICSs: Inhaled Corticosteroids; LABAs: Long-Acting Beta-Agonists; LAMAs: Long-Acting Anticholinergic Agents; QOL: Quality of Life

Introduction

Bronchial asthma is defined according to the American Thoracic Society (1962). This definition emphasizes the functional aspects of asthma, including extensive airway constriction, reversibility, and airway hyperreactivity. However, in recent years, bronchial asthma has been recognized as a chronic airway inflammation involving inflammatory cells, such as T lymphocytes, mast cells, and eosinophils, and is accompanied by organic lesions, such as airway wall remodeling [1].

Chronic Obstructive Pulmonary Disease (COPD) is characterized by obstructive ventilation failure due to chronic bronchitis, emphysema, or both [2]. The disease concepts of bronchial asthma and COPD, characterized by airflow obstruction, have changed historically. Although bronchial asthma and COPD are generally considered distinct diseases, recent research on the immune mechanisms of bronchial asthma suggests that they may not always be completely separate pathologies. As a result, the characteristics of both diseases can overlap and present in similar ways [3].

In 1962, the American Thoracic Society (ATS) coined the term "asthmatic bronchitis" to describe a disease with symptoms of both asthma and COPD. Gobison et al. first proposed the concept of overlap between bronchial asthma and COPD in 2008 [4]. Bronchial asthma is clinically defined as an obstructive respiratory disease characterized by chronic inflammation of the airways, airway narrowing, airway hyper-responsiveness, recurrent coughing, wheezing, and dyspnea. However, it is not a disease that can be diagnosed using an objective index. COPD, on the other hand, is typically diagnosed through spirometry, which shows Forced Expiratory Volume in 1 s (FEV1)/ Forced Vital Capacity (FVC) < 70% after bronchodilator use; however, it should be excluded from other airflow-obstructing diseases. Due

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to the challenge in clearly defining the overlap between asthma and COPD, the term Asthma-COPD Overlap (ACO) has been adopted. Currently, various treatments exist for these diseases [5,6].

The standard treatment for bronchial asthma and COPD involves Inhaled Corticosteroids (ICSs), Long-Acting Beta-Agonists (LABAs), theophylline preparations, and anti-leukotriene antagonists. However, a newer approach known as triple therapy, which combines ICSs + LABAs + Long-Acting Anticholinergic Agents (LAMAs) into a single device, has emerged in recent years. Clinical trials have demonstrated that triple therapy improves respiratory function and reduces exacerbations more effectively than existing treatments [7,8]. However, there is a lack of data on the real-world effectiveness, side effects, and successful cases of these treatments in clinical settings, which could increase physician confidence in prescribing these drugs and explaining their safety and efficacy to patients. Therefore, in our hospital, we examined the changes in Asthma Control Test (ACT) scores and exacerbation rate, which are used to evaluate FEV1 and Quality of Life (QOL) in patients diagnosed with bronchial asthma, COPD, and ACO. Furthermore, we also investigated potential biomarkers for monitoring treatment efficacy.

Methods

Numerous clinical trials have reported that combining ICS + LABA + LAMA inhalation can improve FEV1 and prevent exacerbations in patients with bronchial asthma and COPD, compared to existing treatments. However, there is limited information on the effects and side effects of triple therapy on ACO, with only approximately 14 cases investigated in actual clinical practice [9].

This retrospective study analyzed 311 single-center patients with asthma and ACO who were treated with ICS+LABA+LAMA in addition to their existing treatments. In addition, we investigated the progress of treated patients and determined biomarkers that are effective in predicting efficacy, side effects, and treatment effects, and improving subjective symptoms, using ACT as an example of bronchial asthma. This time, we will discuss the efficacy and safety of triple therapy in the elderly diagnosed with asthma and ACO, which is expected to increase in the future, and what kind of simple biomarkers are available to predict the efficacy of treatment. I will tell you if there is. Real clinical practice data are very informative and taken into account.

Background

This study was conducted retrospectively using anonymized medical records. Prior to the study, patients were provided with sufficient information and explanation about the research, and their personal information was anonymized to protect their privacy. Patients had the option to decline participation if they chose to do so. Therefore, ethics approval was not required.

We included patients receiving triple therapy for COPD, bronchial asthma, or ACO at our hospital between April 2019 and November 2022, based on the diagnostic criteria set forth by the Japanese Respiratory Society [10,11].

Study Population

A total of 311 patients were included in the analysis, and 110 patients were excluded after considering factors such as lack of data, side effects, device failure, and patient refusal, leaving 201 patients for analysis. Of these, 86 had bronchial asthma and 115 had his ACO. (Figure 1) shows the types of drugs the patient received and the background, including her FEV1 before starting triple therapy.

Study 1

In the group diagnosed with ACO, we statistically examined the improvement in peripheral blood eosinophil count, FeNO, IgE, FEV1 and COPD after administration of FF+UME+VI for 6 months.

Study 2

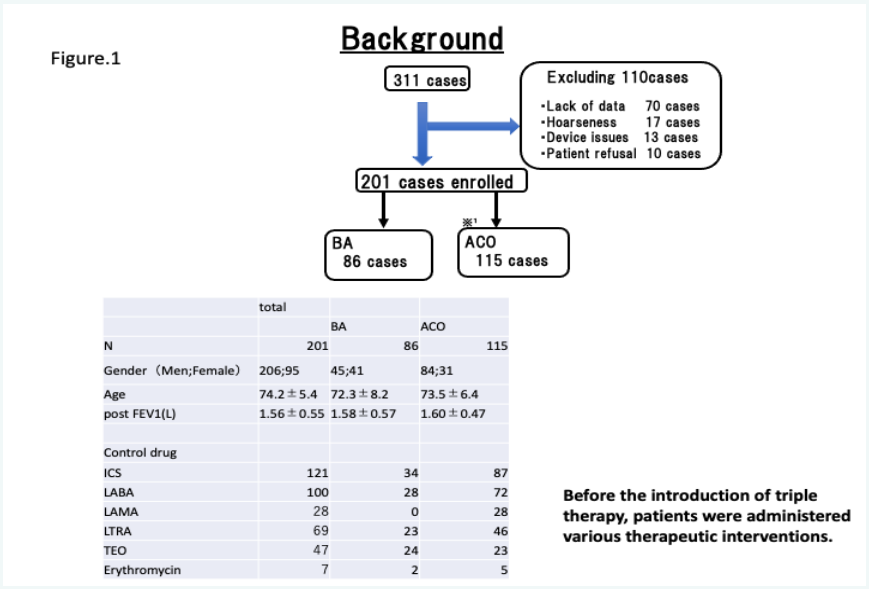
We evaluated the improvement in ACT scores before and after using FF+UME+VI in patients with bronchial asthma. The ACT is an internationally used index of asthma control, scored on a 25-point scale (25 points: complete control, 20-24 points: good control, < 20 points: poor control) [12,13]. Furthermore, by evaluating the correlation between the ACT score and improvement in eosinophil count, IgE, and FeNO at the time of introduction and the improvement in FEV1, we examined whether this correlation can be a biomarker for predicting therapeutic effects. In addition, by examining the correlation between the improvement in eosinophil count, FeNO, and IgE levels and the improvement in FEV1, we assessed whether this correlation can be used as a biomarker for judging therapeutic effects.

Study 3

- Newly diagnosed bronchial asthma
- %FEV1 of < 80
- Untreated asthma
- ACQ7 score of ≥ 1.5
- No asthma attacks at the time of introduction
- Excluding those with smoking history of 10 packs/year
- These cases will be randomized and divided into a FF+UME+VI100 group and a FF+UME+VI200 group to examine the differences in effects in terms of FEV1 and ACT.

Results

In Study 1, FEV1 in all 115 patients diagnosed with bronchial asthma and ACO was 1.56 L in the FF+UME+VI pretreatment group, compared with 1.54 L in the 6-month post-treatment group. The average improvement after changing from existing treatment to triple therapy was 1.83 L. An improvement of approximately 290 mL was observed between groups (Figure 2).



	total	BA	ACO
N	201	86	115
Gender（Men;Female）	206;95	45;41	84;31
Age	74.2±5.4	72.3±8.2	73.5±6.4
post FEV1(L)	1.56±0.55	1.58±0.57	1.60±0.47
Control drug			
ICS	121	34	87
LABA	100	28	72
LAMA	28	0	28
LTRA	69	23	46
TEO	47	24	23
Erythromycin	7	2	5

Figure 1 Research background and patient background..
BA, ACO, asthma-COPD overlap; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in 1 s; ICS: Inhaled Corticosteroid; LABA, Long-Acting Beta-Agonist; LAMA: Long-Acting Anticholinergic Agonist; LTRA: Leukotriene Receptor Antagonist; TEO: Theophylline

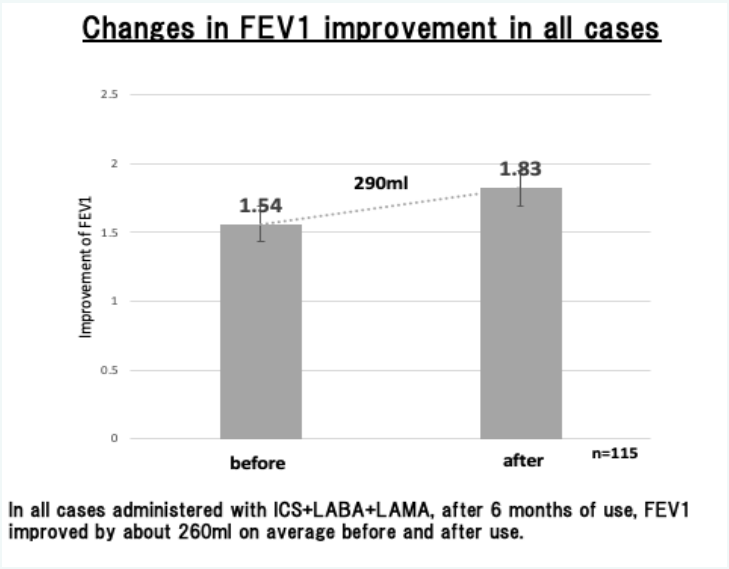


Figure 2 Changes in FEV1 improvement in all patients.
After 6 months of ICS + LABA + LAMA therapy, FEV1 improved by approximately 260 mL on average. FEV1: forced expiratory volume in 1 s; ICS: Inhaled Corticosteroid; LABA: Long-Acting Beta-Agonist; LAMA: Long-Acting Anticholinergic Agonist.

We examined changes in peripheral blood eosinophil count and IgE and FeNO levels, which are considered biomarkers of bronchial asthma. All parameters were improved, with significant differences between the pre- and post-treatment groups (Figure 3). The better the biomarker improvement, the better the FEV1 improvement.

In Study 2, the FEV1 in 86 patients diagnosed with bronchial asthma was 1.58 L in the pretreatment group and 1.92 L in the post-treatment group, indicating that FEV1 improved by approximately 340 mL between the groups (Figure 4). This improvement was significantly better than the results of Study 1, which also included patients with COPD and ACO.

When evaluating QOL, the pre- and post-treatment ACT scores were 14.6 and 19.6 points, respectively-an improvement of 5.0 points (Figure 4). Regarding patients who responded well to triple therapy, we compared the pretreatment values of

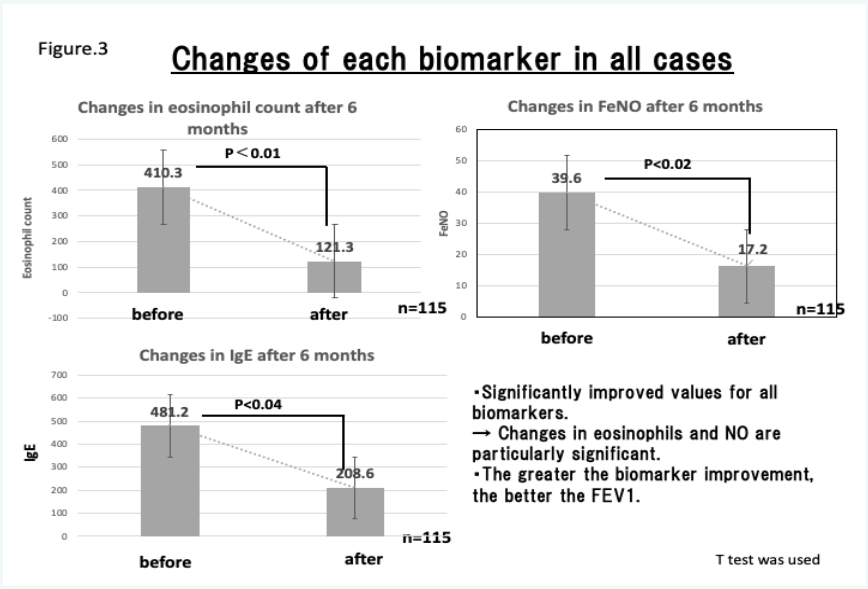


Figure 3 Changes in each biomarker in all patients.
There were significant improvements in all biomarkers. Changes in eosinophils and NO were particularly significant. The greater the biomarker improvement, the better the Forced Expiratory Volume in 1 s (FEV1).

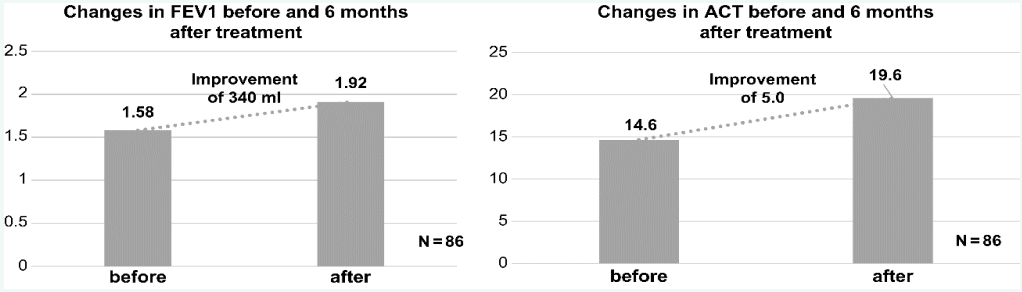


Figure 4 Changes in FEV1 and ACT in bronchial asthma.
Improvement in FEV1 increased further when limited to patients with asthma. The ACT score improved by an average of 5.0 points, and the patient's QOL improved. FEV1: Forced Expiratory Volume in 1 s; ACT: Asthma Control Test; QOL: quality of life.

peripheral blood eosinophil count and FeNO and IgE levels with the improvement in FEV1 and ACT score to examine which items could be used as biomarkers for predicting therapeutic effects. We found that the higher the peripheral blood eosinophil count, FeNO in FEV1, and ACT score at the time of introduction, the greater the improvement. There was a correlation between IgE levels and improvement in FEV1, which can be interpreted as a tendency (Figure 5,6).

Furthermore, when comparing the improvement in each biomarker and the improvement in FEV1 and ACT score, the correlation between peripheral blood eosinophil count and FeNO indicates that these are potential biomarkers for judging therapeutic effects (Figure 7,8). From the above, triple therapy is an effective treatment strategy in patients with a high peripheral blood eosinophil count and FeNO before treatment. Furthermore, peripheral blood eosinophil count and FeNO values can be used to evaluate treatment.

Subjects with newly diagnosed bronchial asthma, %FEV1< 80%, untreated asthma, ACQ7 score ≧ 1.5, no asthma attack at induction, no history of 10 packs of cigarettes per year, were 27 in the FF+UME+VI100 group. Included in the name. We examined the difference in the effects of FEV1 and ACT between 25 cases and the FF+UME+VI200 group (Figure 9). Regarding the results of the FF+UME+VI100 treatment group and the FF+UME+VI200 treatment group, when FEV1 and ACT after 3 months of treatment were compared, the FF+UME+VI200 treatment group was 39.1. FEV1 increased by ml and ACT improved by 4.3 points (Figure 10).

We found that treatment with FF+UME+VI200 contributed to improvement of FEV1 and subjective symptoms in patients with moderate to severe bronchial asthma. Exacerbation occurred in 3 out of 27 cases in the FF+UME+VI100 group and none in the FF+UME+VI200 group. There was no significant difference in side effects, and treatment could be continued if there were no

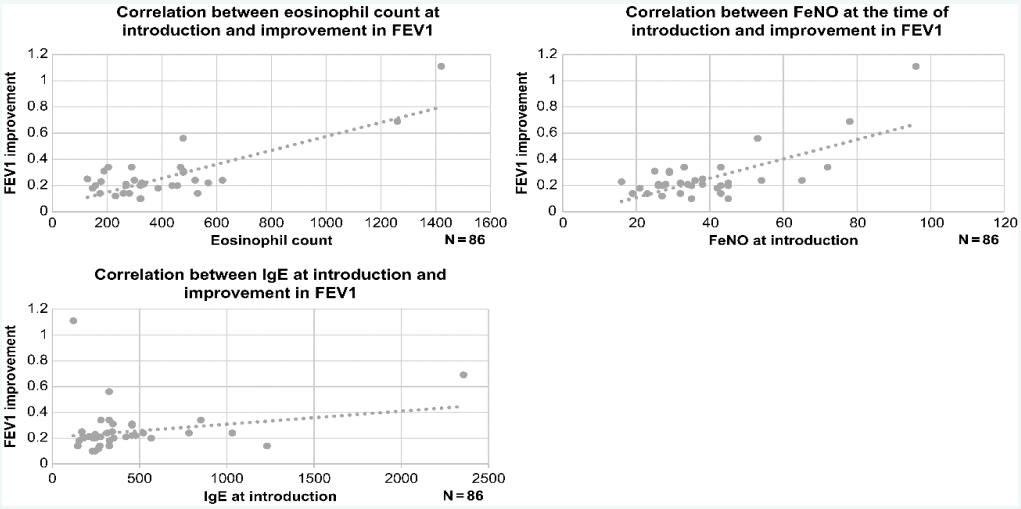


Figure 5 Relationship between the improvement in FEV1 for each biomarker and the eosinophil count at the time of introduction.
The higher the biomarker level at the time of introduction, the more significant the improvement in FEV1; a correlation was observed. FEV1: Forced Expiratory Volume in 1 s.

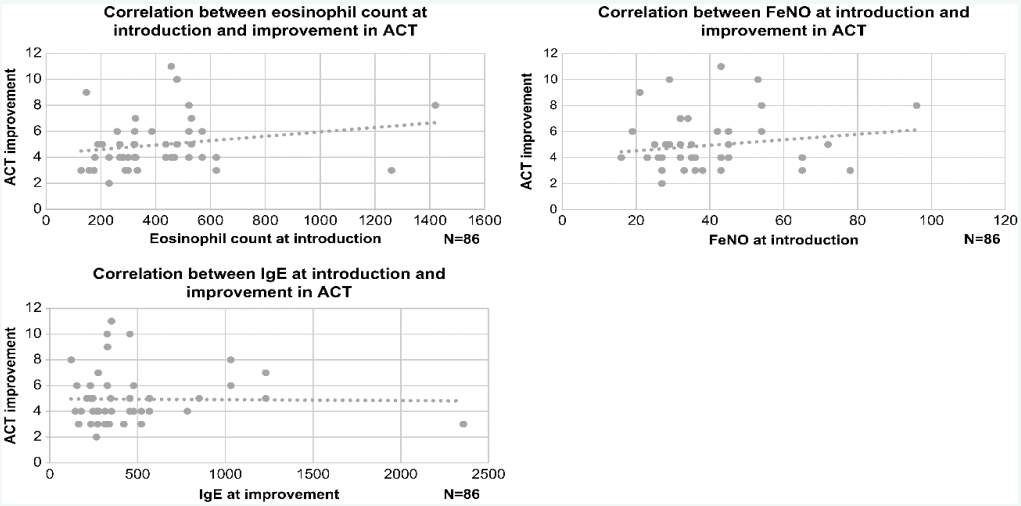


Figure 6 Relationship between each biomarker at the time of introduction and the improvement in ACT score.
The higher the peripheral blood eosinophil count and FeNO at the time of introduction, the greater the improvement in ACT score; a correlation was observed. ACT: Asthma Control Test.

problems with hoarseness or device use within one month after the start of treatment.

Discussion

The data examined at our hospital are not clinical trial data but represent the actual efficacy and side effects of the three-drug combination. As a secondary evaluation, we investigated whether biomarkers can be used to predict and assess treatment efficacy in patients receiving triple therapy. This is the first report examining the efficacy and side effects of ICS + LABA + LAMA single-device inhalers in the real world. The average age of patients examined in this report is approximately 74 years; therefore, this is an important report that shows the usefulness of triple therapy in the future aging society.

When compared to clinical trial data, the results of Studies 1 and 2 tend to show significant improvement. As reported in the real-world CAPTAIN and IRIDIUM trials, the addition of LAMA contributes to a greater degree in improving FEV1 than that contributed by increasing the ICS dose. Previous reports have suggested that the higher the peripheral blood eosinophil count and FeNO, the greater the improvement in FEV1 with the addition of LAMA. The current study also showed that the higher the peripheral blood eosinophil count and FeNO level, the higher the therapeutic effect, demonstrating that the clinical trial reports are consistent with the actual clinical data. Similarly, the

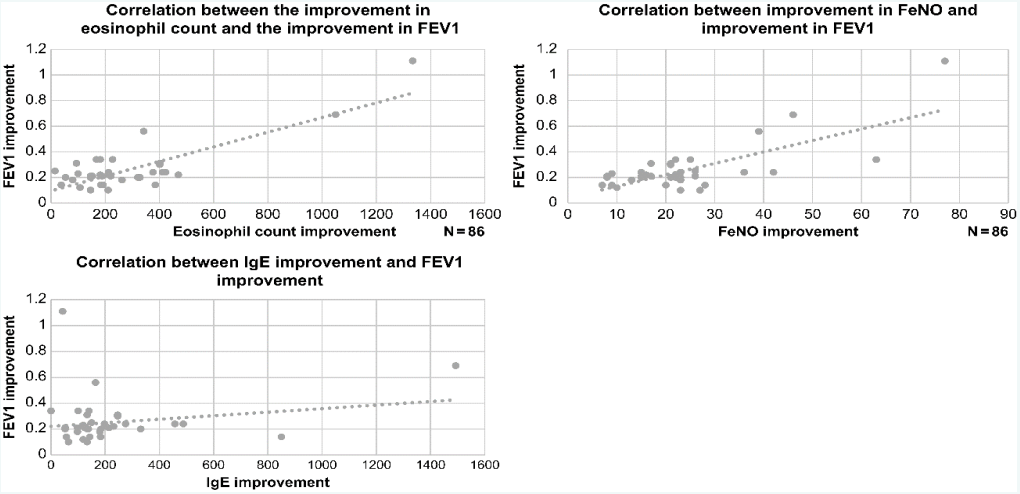


Figure 7 **Relationship between the improvement in each biomarker and the improvement in FEV1.**
The greater the improvement in peripheral blood eosinophil count and FeNO, the greater the improvement in FEV1. FEV1: Forced Expiratory Volume in 1 s.

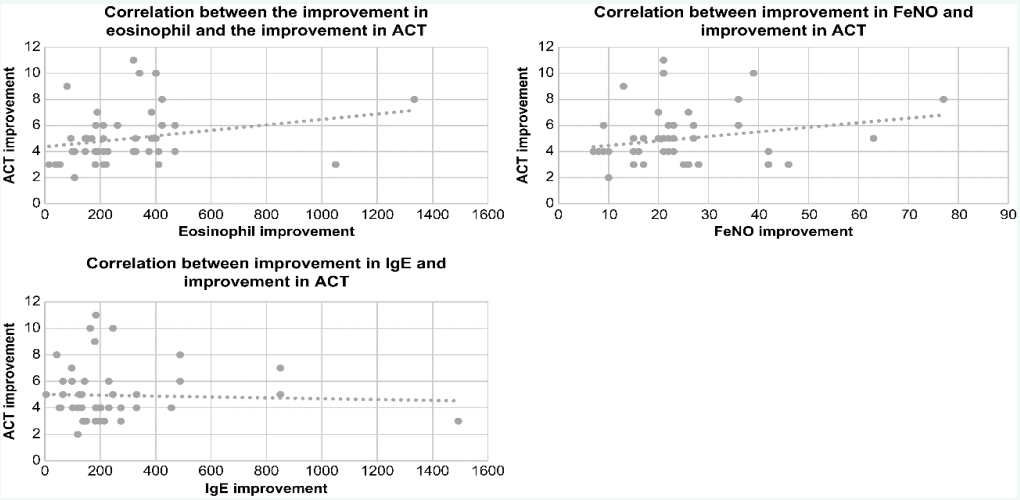


Figure 8 **Relationship between the improvement in each biomarker and the improvement in FEV1.**
Improvements in peripheral blood eosinophil count and FeNO are correlated with ACT score but not with IgE level. FEV1: Forced Expiratory Volume in 1 s; ACT: Asthma Control Test.

ICS + LABA + LAMA treatment group showed superior results compared to existing treatments for bronchial asthma, ACO, ICS + LABA, anti-leukotriene antagonists, and theophylline treatment. The present study also showed that the higher the peripheral blood eosinophil count and FeNO, the higher. The higher the level, the higher the therapeutic effect, indicating that the clinical trial report is consistent with the actual clinical data. Similarly, the ICS + LABA + LAMA treatment arm showed superior results compared to existing therapies for bronchial asthma, ACO, ICS + LABA, antileukotriene antagonist, and theophylline treatment.

Although there are real-world reports of ACO, FEV1 improved to a greater extent with ICS + LABA + LAMA therapy than that with ICS + LABA therapy in only 14 cases [9]. Additional treatment with LAMA can improve FEV1 in patients with bronchial asthma, COPD, and ACO. This is because M3 receptors are expressed in various airway tissues, and acetylcholine binding to these receptors can cause airway smooth muscle contraction, airway submucosal gland mucus secretion, and immune cell inflammation [14]. LAMA blocks these effects, inducing the expansion of smooth muscle and suppression of mucus secretion and inflammatory cells. As a result, peripheral blood eosinophil count and FeNO levels can be used as biomarkers for predicting and judging therapeutic efficacy.

Mouse models of bronchial asthma have an increased amount of acetylcholine in their lungs compared to wild-type mice [15], indicating that LAMA may also be effective in humans. In addition

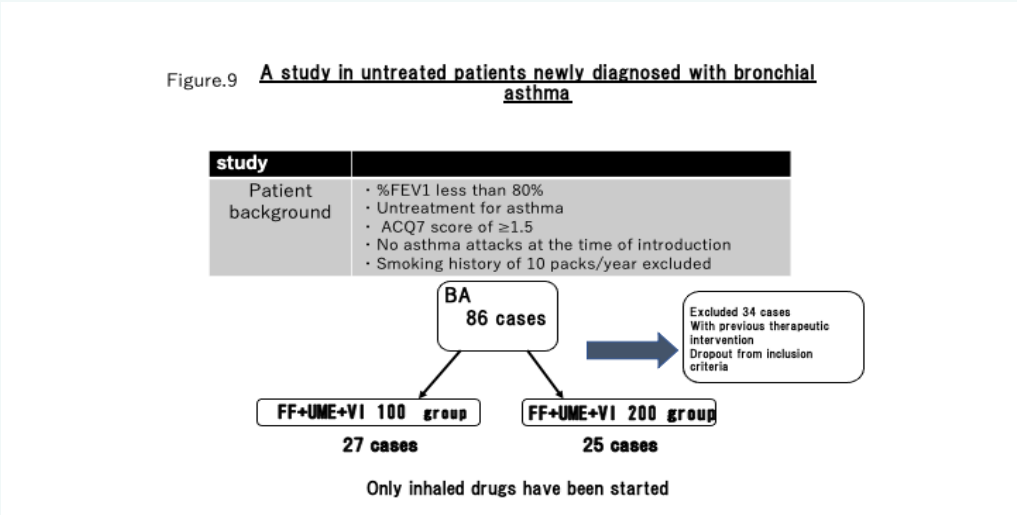


Figure 9 A study in untreated patients newly diagnosed with bronchial astma.
Subjects with newly diagnosed bronchial asthma, %FEV1< 80%, untreated asthma, ACQ7 score ≧ 1.5, no asthma attack at induction, no history of 10 packs of cigarettes per year, were 27 in the FF+UME+VI100 group. Included in the name. We examined the difference in the effects of FEV1 and ACT between 25 cases and the FF+UME+VI200 group.

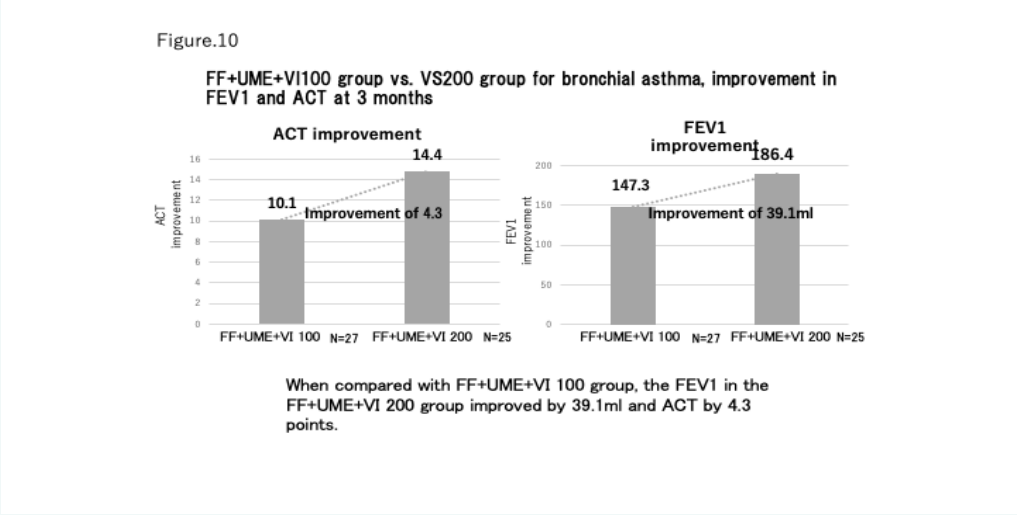


Figure 10 FF+UME+VI100 group VS FF+UME+VI200 group For bronchial asthma, improvement in FEV1 and ACT at 3 months.
Regarding the results of the FF+UME+VI100 treatment group and the FF+UME+VI200 treatment group, when FEV1 and ACT after 3 months of treatment were compared, the FF+UME+VI200 treatment group was 39.1. FEV1 increased by ml and ACT improved by 4.3 points.

to its bronchodilator and bronchostabilizer effects [16], previous research has shown that adherence and efficacy are improved when LAMA therapy is administered using one device rather than multiple devices [17].

The results of Study 3 show that the ICS200 group and the ICS100 group have a large amount of improvement in both ACT and FEV1 in cases with roughly the same level of severity. Since the amount of ICS is high, side effects such as pneumonia will not increase significantly, and it is thought that it will lead to improvement of the patient's QOL.

We believe that this is because ICS has the effect of suppressing airway inflammation, and not only the effect of LAMA but also the synergistic effect of ICS exerts further effects. If you strongly seek therapeutic effects for bronchial asthma and ACO, you should not hesitate to use ICS200 + LABA + LAMA therapy.

Conclusion

A limitation of this study is that it is retrospective in nature. Therefore, premedication could not be arranged prior to triple therapy and the severity of the cases could not be adjusted. Nevertheless, the data from this study provide useful information

for clinicians and patients. We demonstrated the usefulness of LAMA for asthma in the elderly in the clinical setting and demonstrated that peripheral blood eosinophil counts and FeNO are useful in assessing the safety, efficacy and treatment of triple therapy did. In addition, we believe that we were able to demonstrate further therapeutic efficacy and safety by increasing the dose of ICS in the elderly. Further research into the positive effects of LAMA will further improve patient outcomes in the future.

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