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ORIGINAL RESEARCH

Clinical Impact of Mepolizumab on Airway Mucus Plugs in Patients with Severe Asthma

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Purpose: Airway mucus plugs are driven by eosinophilic inflammation and considered an important treatable trait in severe asthma. However, whether mepolizumab, an antibody that suppresses the interleukin-5 pathway and eosinophilic inflammation, can remove mucus plugs remains unclear. The purpose of this study is to evaluate whether mepolizumab treatment could reduce the extent of mucus plugs on computed tomography (CT), and whether changes in mucus plugs were associated with changes in symptoms and pulmonary function following the treatment.

Patients and Methods: This retrospective study included consecutive patients with severe asthma who underwent an asthma control test (ACT), spirometry, and chest CT before and after treatment with mepolizumab at three Japanese hospitals. The mucus plug score (MPS) and total airway count (TAC) were quantified by CT.

Results: Thirty-one (15 male) patients were included in this analysis. Their baseline (pre-mepolizumab) median age, ACT, CT-measured MPS, and TAC were 67 years, 19 points, 7 points, and 232, respectively. Baseline MPS was significantly correlated with forced expiratory volume in one second (FEV1) and TAC (R= −0.39 and R= −0.71, respectively). After treatment with mepolizumab (median 466 days later), median ACT and MPS were 23 points and 1 point, respectively, significantly improved from baseline (both P<0.001). Changes in MPS were significantly correlated with changes in ACT and FEV1 (R= - 0.47 and R= − 0.68, respectively). Furthermore, a higher baseline MPS was significantly associated with greater changes in ACT and FEV1 (R= 0.41 and R= 0.47, respectively).

Conclusion: In this study, mepolizumab treatment coincided with a decrease in MPS, although a direct causal relationship could not be established. Nevertheless, the observed associations between higher baseline MPS and ACT improvement suggest the potential utility of MPS as a biomarker for biological treatment.

Keywords: asthma control test, computed tomography, eosinophilic inflammation, mucus plug score, total airway count

Introduction

Airway occlusion due to mucus plug accumulation, accompanied by goblet cell and submucosal gland hypertrophy, represents a significant pathological feature of severe asthma. Mucus plugs have traditionally been regarded as a characteristic finding in allergic bronchopulmonary aspergillosis (ABPA); however, in patients with asthma, their presence has also been identified as a critical cause of death, alongside bronchospasm, as demonstrated by pathological examinations of 160 autopsy cases.[1–3] Recently, the semi-quantification of airway mucus plugs using chest computed tomography (CT) has been recognized for its clinical relevance in asthma and chronic obstructive pulmonary disease (COPD).[4,5] The severity of mucus plugs, as assessed by chest CT, is inversely correlated with pulmonary function, and extensive mucus plugs are associated with airflow obstruction that is unresponsive to bronchodilators or systemic corticosteroids in patients with asthma.[6,7] Furthermore, conventional asthma treatments, primarily inhalation therapies,

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demonstrate limited efficacy in removing mucus plugs, and persistent mucus plugs for over three years may contribute to an exacerbation-prone phenotype.[8] Although several biologics have been shown to reduce mucus plugs, the clinical characteristics of patients treated with biologics are diverse, necessitating further efforts to optimize treatments for mucus plug reduction to improve outcomes of severe asthma patients.[9–16]

Mepolizumab is a first-in-class humanized monoclonal antibody that binds with high affinity to interleukin (IL)-5, inhibiting its binding to and activation of the IL-5 receptor.[17] Mepolizumab is approved for the treatment of severe asthma with an eosinophilic phenotype, eosinophilic granulomatosis with polyangiitis, and chronic rhinosinusitis (CRS) with nasal polyps in Japan (also eosinophilic COPD approved by Food and Drug Administration).[17–20] In patients with severe asthma, add-on mepolizumab therapy, in conjunction with standard care, reduces exacerbations, decrease oral corticosteroid (OCS) dependence, and improves pulmonary function, asthma control, and health-related quality of life compared with matched placebo in patients with severe eosinophilic asthma with a history of exacerbations, as demonstrated in several clinical trials and real-world experience.[21–25] Despite the growing body of clinical evidence supporting the use of mepolizumab in severe asthma patients, detailed reports of its potential effect on mucus plug reduction remain scarce.

Given that airway mucus plug formation is primarily driven by eosinophilic inflammation, it is hypothesized that suppression of airway eosinophilic inflammation by mepolizumab facilitates the reduction of airway mucus plugs in severe asthma patients.[6] In this study, datasets of chest CT and clinical information before and after mepolizumab treatment in patients with severe asthma were used to evaluate whether mepolizumab treatment could reduce the extent of mucus plugs on CT, and whether changes in mucus plugs were associated with changes in symptoms and pulmonary function following the treatment.

Methods

Study Locations, Enrolled Patients, and Data Collection

In this multicenter, retrospective study, patients with severe asthma who received mepolizumab and underwent CT between 2009 and 2024 at Yokohama City University Hospital, Kyoto University Hospital, and Kitano Hospital were consecutively included. Baseline clinical information, such as smoking history, comorbidities such as CRS, treatment options, asthma control test (ACT) results, blood eosinophil levels, and pulmonary function data including fractional exhaled nitric oxide (FeNO), was gathered from medical records. Respiratory physicians diagnosed asthma according to the Global Initiative of Asthma (GINA) guidelines.[26] An asthma exacerbation is defined as a worsening of asthma requiring the use of systemic corticosteroids for a minimum of 3 days and/or an unscheduled visit to a healthcare provider, emergency department, or hospitalization.[27] Mepolizumab was introduced in patients with severe asthma who experienced asthma exacerbations, depended on regular OCS, and / or severe symptoms despite regular use of ICS and other medications. Mepolizumab was given as a subcutaneous injection of 100 mg every 4 weeks. All patients continued their standard maintenance therapies, as clinically appropriate. Stepwise reduction of ICS potency was considered after confirming the therapeutic efficacy of mepolizumab or when adverse effects associated with high-dose ICS were suspected. The decision to adjust controller medications was made at the discretion of the attending physicians. This study followed the guidelines of the Declaration of Helsinki and was approved by the institutional review board at Yokohama City University Hospital (approval number F231000005) and the ethics committees of Kyoto University (approval number R1660-7) and Kitano Hospital (approval number P210900701). Due to its retrospective nature, the description of the study was provided to all patients on an opt-out basis via the Yokohama City University website (https://yokohama-cu.bvits.com/rinri/publish.aspx). An overview of the study is presented in Figure 1.

Mucus Plug Score (MPS) and Total Airway Count (TAC) Calculated from CT

Full-inspiratory MDCT was conducted in the supine position using Aquilion series scanners (Canon Medical, Otawara, Japan) at Yokohama City University Hospital and Kyoto University Hospital, as well as the Revolution CT scanner (GE Health Care, Milwaukee, WI, USA) at Kitano Hospital. The initial CT within 3 months prior to the initiation of mepolizumab was performed for differential diagnosis of emphysematous changes, eosinophilic lung diseases such as

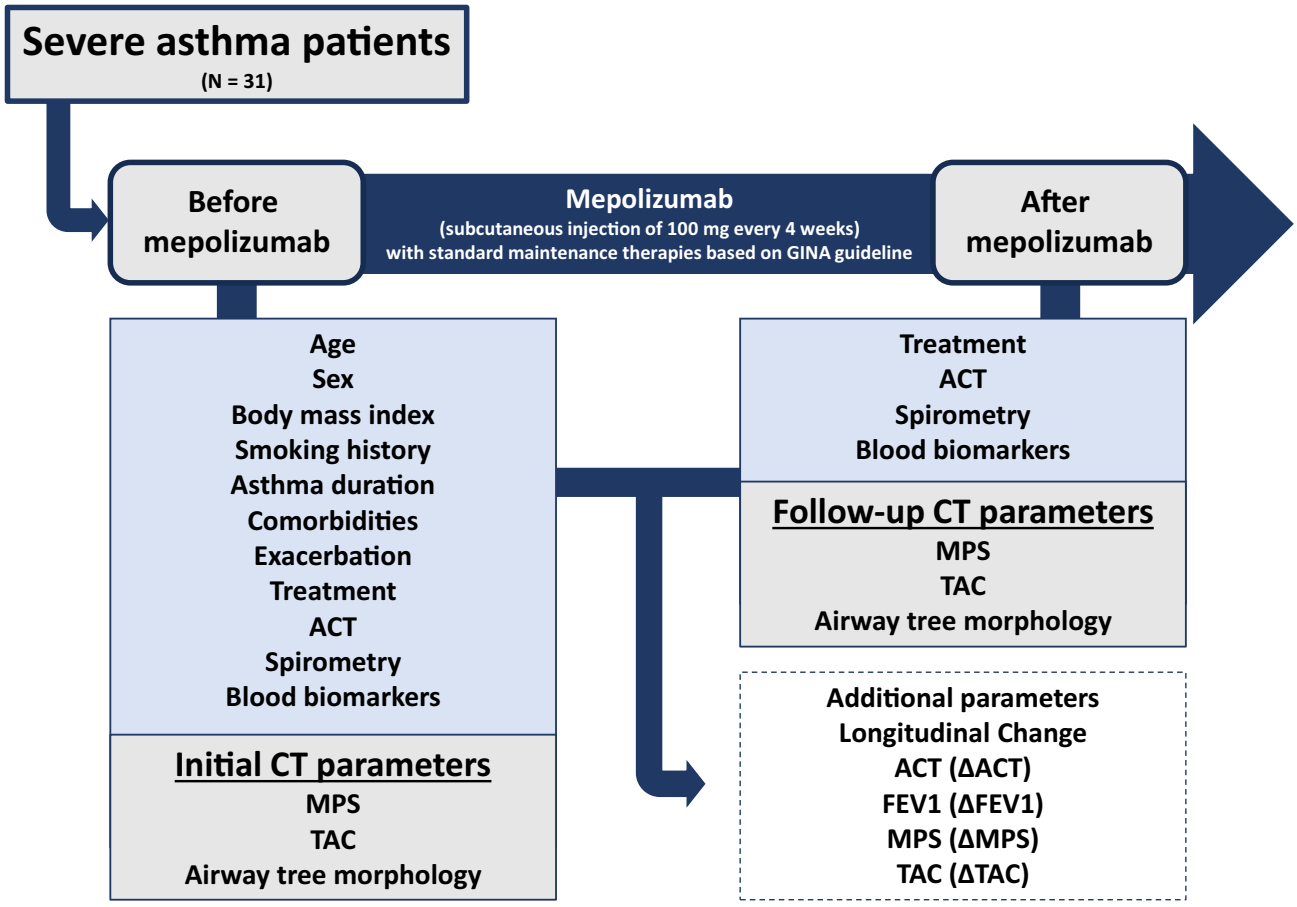

Figure 1 Patients flow diagram. The initial CT within 3 months prior to the initiation of mepolizumab was performed for differential diagnosis of emphysematous changes, eosinophilic lung diseases such as allergic bronchopulmonary aspergillosis and eosinophilic pneumonia, and other chronic pulmonary diseases. The timing of follow-up CT scans is not determined priori.

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in one second; GINA, Global Initiative of Asthma; MPS, mucus plug score; TAC, total airway count.

ABPA and eosinophilic pneumonia, and other chronic pulmonary diseases (Figure 1). At the participating hospitals, each physician is recommended to perform follow-up CT scans to examine the radiological improvement and the development of adverse effects after biologics treatment. However, the timing of follow-up CT scans is not determined priori. Mucus plugs that completely blocked the airway lumen were visually identified and quantified based on the bronchopulmonary segment anatomy, as previously reported.[6] The number of bronchopulmonary segments with at least one mucus plug was recorded as the MPS, ranging from 0 (absence) to 18. The analysis of mucus plugs was carried out by two respiratory physicians (HY and MK) who were blinded to the patients' data. The interrater reliability for MPS was excellent, with an Intraclass Correlation Coefficient of 0.95 (95% Confident Interval: 0.69–0.99). In cases where discrepancies in scores were observed, the final value was determined through consensus. Following the automatic extraction of the airway tree using SYNAPSE VINCENT (Fujifilm Medical Co., Tokyo, Japan), the TAC was determined by extracting the centerline of the luminal tree and counting the number of branches in the skeletonized tree.[28]

Statistical Analysis

Data are shown as medians with the 25th - 75th percentiles or numbers (%). Statistical analysis was performed using JMP12 (SAS Institute, Inc., Cary, NC, USA). Group comparisons were made using Wilcoxon's rank-sum test, the chi-squared test, or paired *t*-test as appropriate. Spearman correlation coefficients were calculated to assess the relationships of ACT, MPS, other clinical parameters and these changes. To identify independent predictors of FEV1 improvement following mepolizumab therapy, multivariable linear regression analysis was conducted using the change of MPS,

baseline MPS, smoking history, body mass index (BMI), and asthma duration as explanatory variables. P values < 0.05 were considered significant.

Results

Baseline Characteristics of Study Patients

A total of 31 patients were included in the analysis, and their baseline characteristics prior to mepolizumab treatment are presented in Table 1. All patients used ICS, and long-acting beta-agonist (LABA). The final maintenance dose of ICS was high-dose in 17 patients (55%) and medium-dose or lower in 14 patients (45%). The prevalence of comorbid CRS, long-acting muscarinic antagonist (LAMA) use, and regular OCS use were observed in 77%, 52%, and 35% of patients, respectively. No cases with concomitant ABPA were observed. Seventeen patients (55%) had ACT scores of 20 or less, and 23 patients (74%) had an MPS of 4 or more. As indicated in Table 2 and Figure 2, the baseline MPS was significantly correlated with forced expiratory volume in one second (FEV1) and TAC.

Table 1 Patients' Characteristics

Variable	N = 31
Age (y)	67 (57–73)
Sex, male (%)	15 (48)
Body mass index, kg/m^2	24.3 (21.0–27.7)
Smoking index, pack-years	0 (0–20)
Never smoker, N (%)	15 (48)
Asthma duration, yrs	13 (3.8–19.5)
Asthma duration ≥ 5 y, N (%)	18 (58)
Annual exacerbation frequency, events/year	1 (0–2)
Asthma control test	19 (13–23)
Chronic rhinosinusitis, N (%)	24 (77)
Treatment before mepolizumab	
ICS, N (%)	31 (100)
LABA, N (%)	31 (100)
LAMA, N (%)	16 (52)
Regular OCS, N (%)	11 (35)
OCS dose (prednisolone equivalent dose), mg/day	0 (0–4)
Pulmonary function test	
Post BD FVC, %predicted, %	89.3 (83.0–98.5)
Post BD FEV1/FVC, %	65.9 (60.1–72.6)
Post BD FEV1, %predicted, %	75.4 (67.9–90.3)
Post BD FEV1, L	1.99 (1.25–2.29)
FeNO, ppb	58 (29.5–97)
Blood biomarkers	
Blood eosinophil ratio, % (normal range, 1–6)	5.2 (2.8–14.3)
Blood eosinophil count, cells/μL	436 (226–950)
(normal range, 100–500)	
CT parameter	
Mucus plug score	7 (3–14)
Total airway count	232 (147–273)

Notes: Data are presented as median (25th–75th percentile) values or numbers (%).
Abbreviations: BD, bronchodilator; CT, computed tomography; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid.

Table 2 Exploration of Baseline Factors Associated with Mucus Plug Score Before Mepolizumab Treatment

Variable	R	95% CI	P Value
ACT	−0.14	−0.47–0.23	0.468
FVC, %predicted	−0.10	−0.45–0.27	0.591
Post BD FEV1/FVC	−0.18	−0.51–0.20	0.346
Post BD FEV1, %predicted	−0.24	−0.56–0.14	0.210
Post BD FEV1	−0.39	−0.66 - −0.03	0.034
Blood eosinophil count	0.03	−0.33–0.38	0.868
Blood eosinophil ratio	0.17	−0.19–0.49	0.363
FeNO	0.05	−0.35–0.44	0.801
Total airway count	−0.71	−0.86 - −0.45	< 0.001

Notes: Asthma control test (ACT), post-bronchodilator spirometry (forced vital capacity [FVC] and forced expiratory volume in one second [FEV1]), fractional exhaled nitric oxide (FeNO), and total airway count on computed tomography were measured in 31, 29, 25, and 23 patients, respectively.

Longitudinal Changes in Clinical and Computed Tomography Parameters Following Mepolizumab Treatment

As presented in Table 3 and Figure 3, the ACT score and FEV1 increased and MPS decreased significantly following mepolizumab treatment (median follow-up of 466 (28–1758) days, mean follow-up of 591±477 days), whereas TAC did not significantly change. Accordingly, the regular OCS dose, expressed as prednisolone equivalent, decreased from 1.88 mg to 1.79 mg. A reduction in OCS dosage was observed in 9 out of 11 patients (81%). Also, as shown in Table 4 and Figure 4, the baseline MPS was significantly associated with changes in the ACT score, FEV1, and MPS. The change

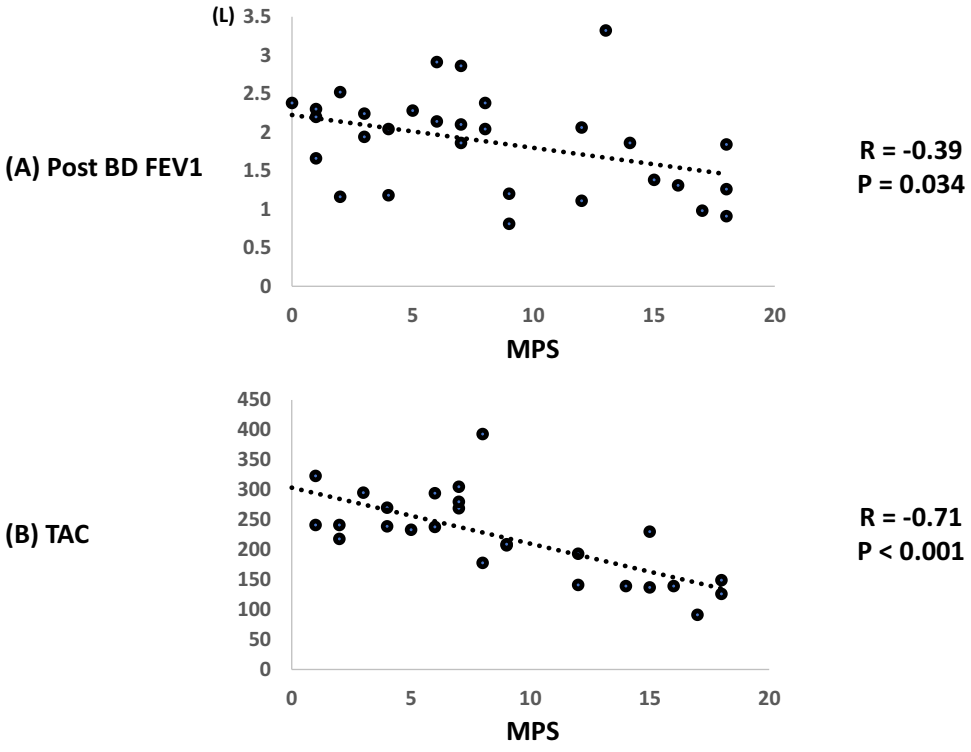

Figure 2 Relationships between baseline mucus plug scores and clinical-functional-radiological parameters. The baseline MPS are significantly correlated with the baseline FEV1 (R = −0.39, P = 0.034 (**A**)) and TAC (R = −0.71, P < 0.001 (**B**)).
Abbreviations: FEV1, forced expiratory volume in one second; MPS, mucus plug score; TAC, total airway count.

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Table 3 Longitudinal Changes in Clinical and CT Parameters Following Mepolizumab Treatment

Variable	Before Mepolizumab	After Mepolizumab	P Value
ACT	19 (13–23)	23 (19–25)	< 0.001
Post BD FEV1, L	1.99 (1.25–2.29)	2.14 (1.51–2.42)	0.010
MPS	7.0 (3.0–14.0)	1.0 (0.0–5.0)	< 0.001
TAC	232 (147–273)	262 (205–358)	0.052

Notes: Data are presented as median (25th – 75th percentile) values. Changes in asthma control test (ACT) and mucus plug score (MPS) were measured in 31 patients whereas those in forced expiratory volume in one second (FEV1) and total airway count (TAC) were measured in 29 and 26 patients, respectively.

in MPS was significantly associated with changes in the ACT score and FEV1, but not with TAC, as shown in Figure 5. Furthermore, in the multivariable linear regression analysis, the change in mucus plug score (ΔMPS) was identified as the strongest independent predictor of improvement in FEV1 following mepolizumab treatment. In contrast, baseline MPS, smoking history, BMI, and asthma duration showed no significant associations ($p > 0.05$ for all) (Table 5).

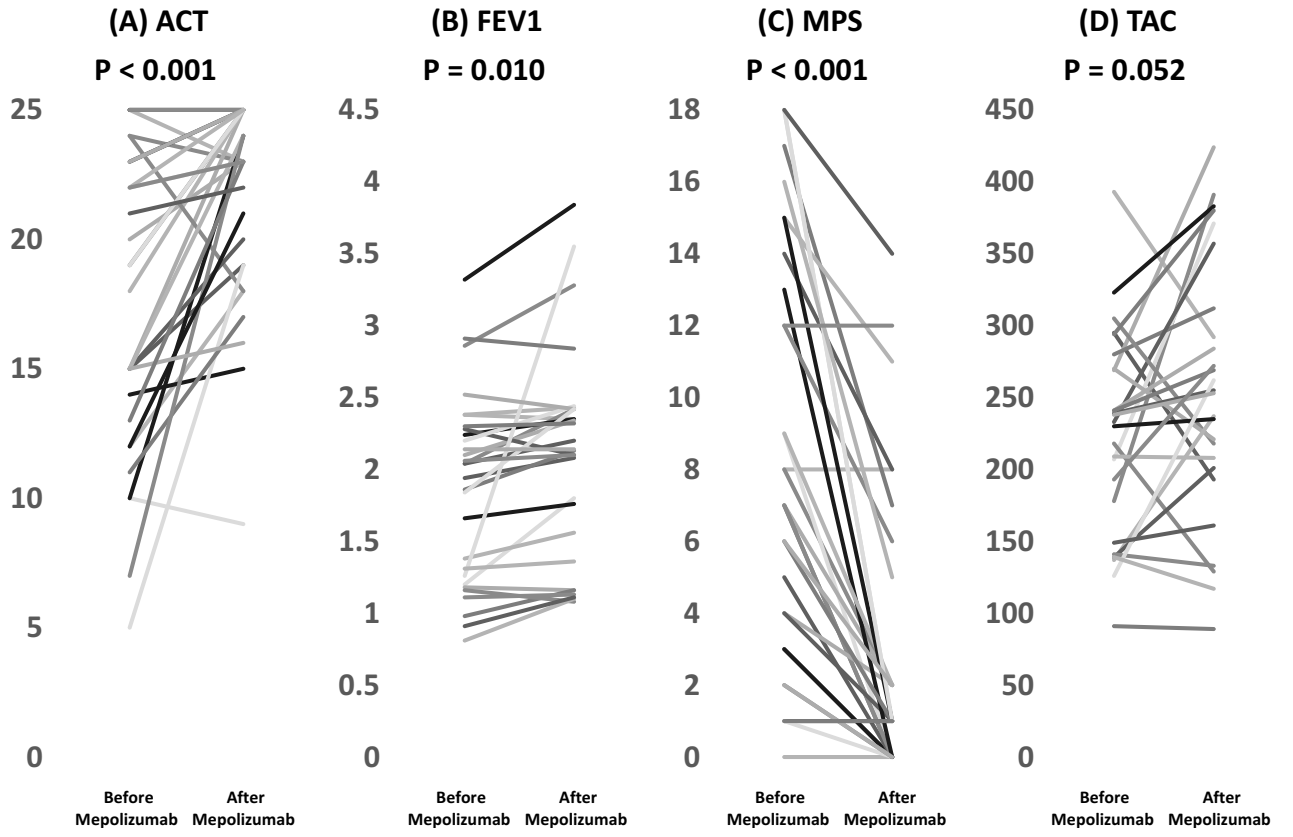

Figure 3 Longitudinal changes in symptoms, pulmonary function and CT parameters following mepolizumab treatment. (**A**) Change in ACT after mepolizumab: ACT scores show a significant increase after mepolizumab (P < 0.001). Median ACT before mepolizumab: 19 (13–23); Median ACT after mepolizumab: 23 (19–25). (**B**) Change in FEV1 after mepolizumab: FEV1 values increase significantly after mepolizumab (P = 0.010). Median FEV1 before mepolizumab: 1.99 (1.25–2.29) liters; Median FEV1 after mepolizumab: 2.14 (1.51–2.42) liters. (**C**) Change in MPS after mepolizumab: MPS values decrease significantly after mepolizumab (P < 0.001). Median MPS before mepolizumab: 7.0 (3.0–14.0); Median MPS after mepolizumab: 1.0 (0.0–5.0). (**D**) Change in TAC after mepolizumab: TAC values tend to increase after mepolizumab (P = 0.052). Median TAC before mepolizumab: 232 (147–273); Median TAC after mepolizumab: 262 (205–358).
Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in one second; MPS, mucus plug score; TAC, total airway count.

Table 4 Associations of Baseline Mucus Plug Score with Longitudinal Changes in Pulmonary Function, Symptom, and CT Parameters After Mepolizumab Treatment

Variable	R	95% CI	P Value
ΔACT	0.41	0.06–0.67	0.023
ΔFEV1	0.47	0.12–0.71	0.010
ΔMPS	−0.74	−0.86 - −0.52	< 0.001
ΔTAC	0.16	−0.23–0.52	0.427

Notes: Changes in asthma control test (ACT) and mucus plug score (MPS) were measured in 31 patients whereas those in forced expiratory volume in one second (FEV1) and total airway count (TAC) were measured in 29 and 26 patients, respectively.

Comparison of MPS Before and After Mepolizumab by Clinical Background

To identify clinical background characteristics associated with more pronounced mucus plug reduction, asthma duration, comorbid conditions, blood biomarkers, pulmonary function, and CT parameters were evaluated in relation to the presence or absence of reductions in MPS before and after mepolizumab, as well as the rate of change. As shown in Table 6, no significant reduction in the MPS was observed in patients with FeNO levels ≤ 30 ppb, whereas significant reductions were noted in all other subgroups. In addition, a greater likelihood of MPS reduction was observed in patients

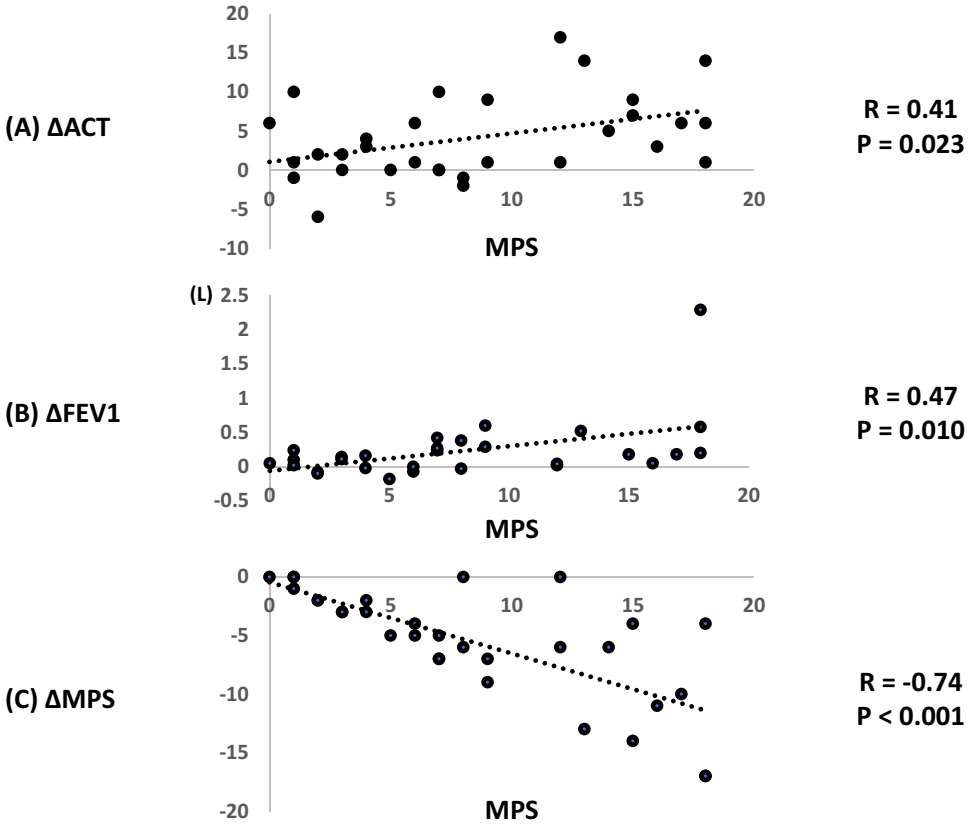

Figure 4 Relationships between baseline mucus plug scores and longitudinal changes in clinical-functional-radiological parameters following mepolizumab treatment. The baseline MPS are significantly correlated with the changes in ACT (R = 0.41, P = 0.023 (**A**)), FEV1 (R = 0.47, P = 0.010 (**B**)) and MPS (R = −0.74, P < 0.001 (**C**)).
Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in one second; MPS, mucus plug score.

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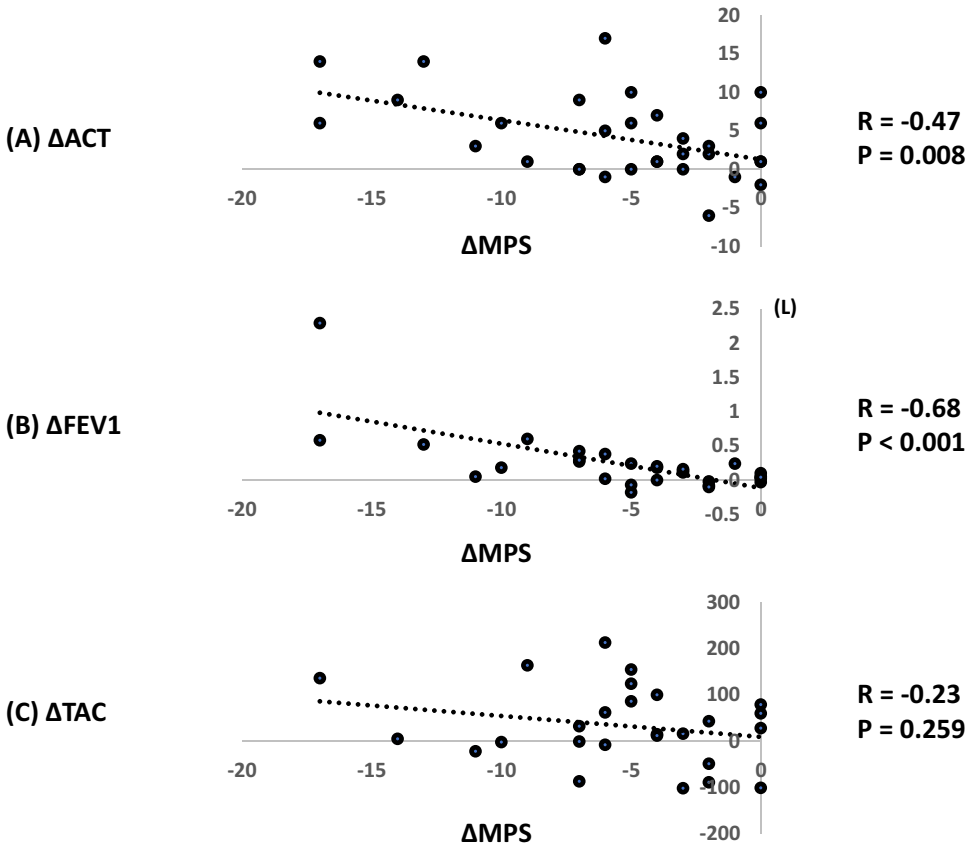


Figure 5 Relationships between longitudinal changes in mucus plug scores and clinical-functional-radiological parameters following mepolizumab treatment. The changes in the MPS are significantly correlated with the changes in ACT (R = −0.47, P = 0.008 (**A**)) and FEV1 (R = −0.68, P < 0.001 (**B**)), but not with the change in TAC (R = −0.23, P = 0.259 (**C**)).
Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in one second; MPS, mucus plug score; TAC, total airway count.

with an asthma duration of less than five years, comorbid CRS, blood eosinophil count ≥ 300 cells/μL, FeNO > 30 ppb, and FEV1/FVC ≥ 70%.

Three-Dimensional Representation of Pulmonary Airways

Figure 6 shows a three-dimensional representation of airway tree morphology before and after mepolizumab for two representative participants. In both cases, airway tree defects caused by airway narrowing due to mucus plugs were ameliorated following mepolizumab administration, accompanied by substantial improvements in the ACT score, MPS, and TAC.

Table 5 Multivariable Models for the Associations of Change in Mucus Plug Score with Change in Pulmonary Function After Mepolizumab Treatment

Variable	Model 1	Model 2	Model 3	Model 4
ΔMPS	−0.069 (−0.11, −0.03)*	−0.032 (−0.05, −0.02)*	−0.027 (−0.05, −0.01)*	−0.029 (−0.04, −0.01) *
Baseline MPS	−0.005 (−0.04, 0.03)	–	–	–
Pack-years	-	0.001 (−0.01, 0.01)	-	-
Asthma duration	-	-	−0.002 (−0.01, 0.01)	-
BMI	-	-	-	−0.001 (−0.02, 0.01)

Notes: Each linear regression models included a change in mucus plug score from baseline to after mepolizumab treatment (ΔMPS) and either baseline MPS, smoking pack year, asthma duration, or body mass index (BMI) as independent variables and a change in forced expiratory volume in one second from baseline to after treatment as a dependent variable. * p<0.05.

Table 6 Changes in Mucus Plug Score from Before to After Mepolizumab Treatment Stratified by Clinical Background

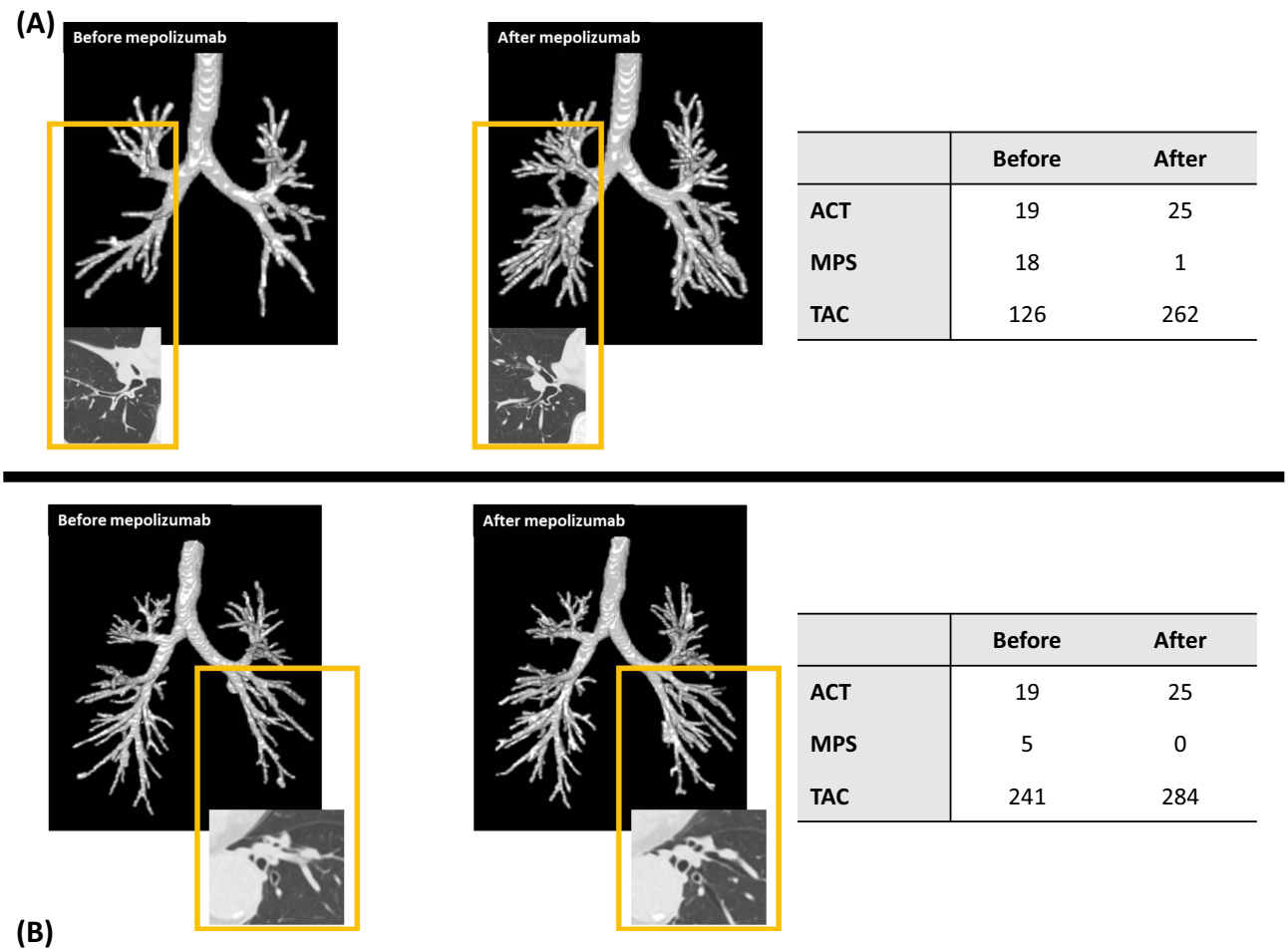
Variable	MPS Before Mepolizumab	MPS After mepolizumab	Volatility	P Value
Asthma duration < 5 y, N = 13	12.5 (4.5–12.5)	1 (0–2)	−64%	< 0.001
Asthma duration ≥ 5 y, N = 18	6.5 (2.8–15.5)	1 (0–8)	−57%	< 0.001
CRS (+), N = 24	6.5 (2.8–15.5)	0 (1–8)	−71%	< 0.001
CRS (-), N = 7	9 (8–12)	2 (1–6)	−57%	0.026
BEC < 300, N = 13	6 (2.5–10.5)	1 (0–5)	−63%	0.003
BEC ≥ 300, N = 18	8.5 (3.8–16.3)	1 (0–5.3)	−72%	< 0.001
FeNO ≤ 30, N = 7	8 (2–15)	1 (0–11)	−71%	0.053
FeNO > 30, N = 18	7 (4.8–16.3)	1 (0–2.8)	−74%	< 0.001
FEV1/FVC < 70%, N = 19	8 (4–14)	2 (1–8)	−60%	< 0.001
FEV1/FVC ≥ 70%, N = 10	5.5 (1.8–10.5)	1 (0–1)	−83%	0.004
TAC < 231 (median), N = 13	14 (9–16.5)	5 (1–9.5)	−62%	< 0.001
TAC ≥ 231 (median), N = 13	5 (2.5–7)	1 (0–2)	−65%	< 0.001

Notes: Data are presented as median (25th – 75th percentile) values or numbers. Mucus plug score (MPS) were compared between before and after mepolizumab treatment. Patients were dichotomized based on asthma duration of 5 years (5 y), chronic rhinosinusitis (CRS), blood eosinophil count (BEC) of 300 /μL, fractional exhaled nitric oxide (FeNO) of 30 ppb, % of forced expiratory volume in one second / forced vital capacity (FEV1/FVC) of 70%, and median total airway count (TAC) of 231 on CT.

Discussion

Evidence for the reduction of mucus plugs by biologic agents, primarily benralizumab, dupilumab, and tezepelumab, has been reported.[11–16] In the Phase 4 VESTIGE trial (NCT04400318), adults with uncontrolled, moderate-to-severe type 2 asthma were randomized to receive dupilumab or placebo for 24 weeks. Dupilumab significantly increased the proportion of patients achieving FeNO <25 ppb (57% vs 11%) and showed numerical improvement in airway volume assessed by functional respiratory imaging. Treatment reduced airway inflammation and mucus plugging, with a safety profile consistent with previous reports.[14] In the CASCADE trial (NCT03688074), tezepelumab significantly reduced mucus plug burden on CT compared with placebo in patients with moderate-to-severe asthma. Baseline mucus plug extent correlated with type 2 inflammation biomarkers and inversely with pulmonary function, and reductions in plug scores accompanied improvements in airflow and eosinophilic activity.[16] In the present study, mepolizumab treatment significantly reduced the MPS, and this reduction was associated with improvements in the ACT score and FEV1. In addition, a higher baseline MPS was significantly correlated with improvements in the ACT score and FEV1. To the best of our knowledge, this is the first study to show the effect of mepolizumab on mucus plug removal and airway tree morphology assessed as TAC on CT.

Type 2 cytokines, including IL-5 and IL-13, are thought to contribute to the progression of airway wall remodeling and the development of mucus plugs. IL-13 enhances hydrogen peroxide production and stimulates the secretion of MUC5AC-rich mucus by the airway epithelium. IL-5 promotes the recruitment of eosinophils containing eosinophil peroxidase and supports their accumulation and survival within the cysteine-rich mucin environment. Moreover, enhanced eosinophil peroxidase increases the viscosity of mucus plugs through mucin crosslinking. Indeed, a recent ultra-high-resolution CT study showed that a higher blood eosinophil count was positively correlated with mucus plug density.[29] In addition to the mucus plug reduction by mepolizumab treatment after a median of 466 days in this study, a study by Sasaki et al showed that the anti-IL-5 receptor antibody, benralizumab, reduced the MPS at 4 months after the initiation of treatment in 12 patients with severe asthma.[11] Moreover, McIntosh et al demonstrated significant improvements in the MPS, TAC, and 129Xe MRI ventilation defect over 2.5 years in 13 patients.[12] We speculate that suppression of eosinophilic inflammation by mepolizumab could reduce the viscosity of mucus plugs and facilitate their clearance from the airways. Given that the present sample size was comparable to the previous studies,and that evidence for the efficacy of mepolizumab in mucus plug reduction is limited, the present findings represent a valuable contribution to the literature.[11,12] Although no correlation was observed between the interval from the initial CT to the follow-up CT and the change in MPS in this study, frequent assessment of MPS using CT is impractical in routine



	Before	After
ACT	19	25
MPS	18	1
TAC	126	262

	Before	After
ACT	19	25
MPS	5	0
TAC	241	284

Figure 6 Three-dimensional representation of pulmonary airways. The three-dimensional depiction of pulmonary airways, resembling an airway tree, and the MPS are shown before and after mepolizumab treatment. Yellow boxes highlight mucus plugs that have been clearedafter mepolizumab treatment. In Case 1, the subject is a 58-year-old woman with CRS at enrollment (**A**). In Case 2, the subject is a 78-year-old man at enrollment (**B**).
Abbreviations: ACT, asthma control test; CRS, chronic rhinosinusitis; MPS, mucus plug score; TAC, total airway count.

clinical practice. Therefore, the timing at which mucus plug reduction becomes evident remains unclear. Given that intraluminal mucus plugs are a key pathological feature in severe asthma, the development of surrogate markers for MPS is likely to be of significant clinical importance.

TAC is considered an important imaging biomarker in obstructive lung diseases.[30–32] In a study by Tanabe et al of COPD, the MPS and TAC were complementarily associated with airflow limitation, health-related independence, and mortality.[30] Whereas TAC is measured based on visible airway branches on CT, it may be predictive of the number of terminal bronchioles visible on micro-CT, but not on CT.[31] In a study of patients with asthma, decreased TAC was associated with increased asthma severity, wall area, and ventilation defects.[32] Notably, despite the observed significant association between the baseline MPS and TAC prior to mepolizumab treatment, TAC did not show a significant increase following mepolizumab treatment, unlike the MPS. Furthermore, the MPS reduction was not associated with an increase in TAC; the MPS decreased regardless of TAC levels. These discrepant findings in TAC and MPS may be because TAC captures small airway dysfunction more strongly than the MPS, which correlates with FEV1, a sensitive indicator of central airway narrowing.[33] Therefore, the MPS and TAC may reflect distinct aspects of the pathophysiological features, and thus their use in combination would be important in the management of severe asthma. Furthermore, airway tree morphology assessed as TAC on CT may be highly useful in visually evaluating the therapeutic efficacy of mepolizumab.[34] The clinical significance of airway tree morphology in obstructive lung diseases remains an important subject for future investigation.

ACT is used extensively for assessing the efficacy of biologic agents.[35,36] The observed correlations between a higher baseline MPS and subsequent improvement in ACT scores align with the findings of Götschke et al, who demonstrated that a higher MPS was associated with more significant changes in both ACT scores and FEV1 following biologic treatments.[37] These results imply that mucus plugs may represent a modifiable characteristic in severe asthma that can be addressed through biologic intervention. However, ACT is influenced not only by mucus obstruction but also by multiple other factors, including airway hyperresponsiveness, inflammation, and airway remodeling.[38,39] Therefore, the improvement in ACT should not be interpreted as a direct surrogate of mucus plug reduction alone, but rather as a composite reflection of overall disease amelioration.

This study further demonstrated that more significant reductions in the MPS were observed in patients with an asthma duration of less than five years, who also had better preserved pulmonary function. Given that the progression of refractory asthma involves mucus plug formation as an early effect and airway remodeling as a late effect, these findings highlight the critical importance of accurate diagnosis of severe asthma and the early initiation of biologic therapy.[40] However, this study did not include longitudinal follow-up of parameters such as MPS or FEV1, and therefore it remains unclear whether the degree of mucus plug reduction is associated with long-term preservation of pulmonary function. Accordingly, longitudinal investigations into structural airway changes - including MPS on CT scans - after mepolizumab administration, in relation to asthma duration, represent an important direction for future research.

Several limitations warrant consideration. First, due to the retrospective nature of this study, along with a small number of cases with FeNO levels below 30 ppb due to their low prevalence, the generalizability of the findings may be limited. Larger prospective cohort studies are necessary. Second, the interval between baseline and follow-up CT scans after mepolizumab administration was not standardized, complicating the understanding of the temporal progression of mucus plug reduction. Also, the timing of repeat CT was determined at the discretion of the attending physicians. Third, the effects of mepolizumab on peripheral airway mucus plugs and structural changes remain unassessed due to the limited resolution of CT images. Fourth, though improvements in the MPS may serve as a significant biomarker for predicting clinical remission, they are likely inadequate for forecasting disease resolution. Further comprehensive investigations are needed to identify biomarkers predictive of long-term remission, particularly from the results of ongoing prospective cohort studies currently being conducted in Japan.[41]

Conclusion

This retrospective study suggests that mepolizumab treatment may be associated with a reduction in airway mucus plugs in patients with severe asthma, although a causal relationship cannot be established. Mucus plugs constitute an important treatable trait in severe asthma, and MPS and TAC obtained from CT may provide useful imaging biomarkers for assessing treatment response.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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