

Perspective

Statin as Regulatory T Cell Modulator in COPD With Early Disease

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Keywords: COPD; regulatory T cell; granzyme B+ cell; statin

Abbreviations: COPD = chronic obstructive pulmonary disease; Treg cell=regulatory T cell; CD =cluster of differentiation; FEV₁ =forced expiratory volume in 1 second; CLE=centrilobular emphysema; Gzm B=granzyme B; BAL=bronchoalveolar lavage; FOXP3=forkhead box P3; NK cell=natural killer cell; CCl₄=carbon tetrachloride.

Funding Support: None.

Date of Acceptance: September 1, 2026 | **Published Online Date:** September 30, 2026

Citation: Kim WD, Sin DD. Statin as regulatory T cell modulator in COPD with early disease. *Chronic Obstr Pulm Dis*. 2026; Published online September 30, 2026.
<https://doi.org/10.15326/jcopdf.2026.0776>

Abstract

Early detection and intervention are critical to preventing or slowing the progression of COPD to advanced stages. However, no disease-modifying agent is currently available. COPD smokers exhibit reduced regulatory T (Treg) cell levels in lung tissue, whereas normal smokers demonstrate higher levels. Treg cells may mitigate lung damage by suppressing cytolytic CD8⁺ T-cells. Forced expiratory volume in 1 second (FEV₁) correlates with Treg cell levels in COPD. In lung tissue from surgically removed centrilobular emphysema lungs, granzyme (Gzm) B⁺ cells correlated with FEV₁. Gzm B is considered a potential functional marker for Treg cells. An animal study found that statins increase Treg cell proliferation and Gzm B secretion. Statins are known to increase Treg cell activity in human. This review synthesized clinical evidence on the immunomodulatory effects of statins in COPD, with particular emphasis on disease stage, duration of treatment, and timing of statin initiation relative to smoking exposure. Findings from prospective clinical trials in COPD have been inconsistent. In contrast, retrospective studies have demonstrated apparent advantages of statins. Notably, participants in prospective trials often had more advanced airflow limitation and shorter durations of statin exposure. Experimental evidence in animals indicates that statin administration initiated 3 months after smoking was ineffective, whereas treatment commenced at the onset of exposure attenuated airway disease. These findings suggest that statin therapy may have disease-modifying potential when initiated in COPD patients with early disease. Prospective trials focusing on this population are urgent to determine whether statins can prevent or slow disease progression of COPD.

Introduction

Globally, chronic obstructive pulmonary disease (COPD) is a leading cause of long-term morbidity and mortality. Owing to aging populations and ongoing exposure to risk factors such as air pollution and tobacco use, the burden of COPD is expected to increase in the future decades.¹ However, new opportunities for early diagnosis, and timely and appropriate therapeutic intervention for COPD prevention, are made possible by the understanding that environmental factors beyond tobacco smoking contribute to the disease development, that COPD can begin early in life and affect young people, and that precursor conditions exist.² Notably, patients with mild COPD in general exhibit a faster annual decline in forced expiratory volume in 1 second (FEV₁) compared with those with severe disease.³ Early intervention is therefore essential, as the reversibility of airflow limitation is limited to the early stages. Identifying strategies to modify disease progression in early-stage COPD is critical. However, currently no disease-modifying agent exists to prevent or slow lung function decline in COPD.

Potential role of regulatory T cells in COPD progression

A recent systematic review of 48 studies on the role of cluster of differentiation 8 (CD8+) T cells in COPD reported that not only an increase in CD8+ T cell numbers but also enhanced effector function, likely contributing to disease pathogenesis.⁴ Patients with COPD have lower levels of regulatory T (Treg) cells in bronchoalveolar lavage (BAL) fluid than in normal smokers, suggesting that insufficient Treg cell-mediated suppression of cytolytic CD8+ T cells may facilitate disease progression.⁵ In contrast, smokers with preserved lung function exhibit substantial upregulation of Treg cells, which is absent in smokers with COPD. This finding

indicates a diminished Treg cell response to tobacco smoking in patients with COPD. Treg cell upregulation in smokers with normal lung function likely suppresses smoke-induced inflammation, whereas the absence of this mechanism in smokers with COPD may exacerbate the inflammatory response, accelerating disease progression.

More recently, nine studies investigating Treg cells in the small airways, alveoli, lung tissue, bronchial mucosa, or BAL fluid consistently demonstrated fewer Treg cells in smokers with COPD compared with normal smokers or nonsmokers, as well as lower Treg cells or forkhead box P3 (*FOXP3*) gene expression in the peripheral blood of patients with COPD.⁶ Moreover, three studies have demonstrated a significant association between Treg cell counts in the lung tissue or BAL fluid and FEV₁% predicted.⁷⁻⁹ These findings indicate that Treg cell availability may determine the extent of airflow limitation in patients with COPD. A longitudinal study further demonstrated that Treg cells in BAL fluid were inversely correlated with the rate of lung function decline over 5 years.¹⁰ Collectively, these results support a critical role for Treg cells in the pathogenesis of COPD, with their relative deficiency linked to disease onset and progression to more severe stages.¹¹

Granzyme B-positive cells in lung tissue of centrilobular emphysema

Out of surgically resected lungs for lung tumor or transplantation, selected lung tissues with microscopically confirmed various degrees of centrilobular emphysema (CLE) underwent immunohistochemical staining using antibodies against CD8 and granzyme B (GzmB).^{12,13} The findings demonstrated that the quantity of GzmB-positive (GzmB+) cells/mm² in the alveolar walls (Figure 1A)¹³ and the volume fraction (defined as the volume of stained cells per unit

tissue volume) of GzmB⁺ cells in the small airways¹² were significantly correlated with FEV₁% predicted. Furthermore, lung tissue expression of GzmB, quantified by an enzyme-linked immunosorbent assay, was positively correlated with the FEV₁% predicted in smokers with FEV₁ < 80% predicted.¹²

This close relationship between both the number of alveolar GzmB⁺ cells and the volume fraction of GzmB⁺ cells in the small airways and FEV₁% predicted was similar to previously reported correlations between the number of Treg cells in lung tissue or BAL fluid and FEV₁% predicted in patients with COPD.⁷⁻⁹ This finding raises the possibility that the GzmB⁺ expressions in lung tissue may determine the extent of lung damage and, consequently, the severity of airflow limitation. Additionally, tissue presence of alveolar GzmB⁺ cells was significantly higher in cases with FEV₁ ≥ 80% predicted than in those with FEV₁ < 80% predicted (Figure 2A). Interestingly, however, in the same study, there was no difference in the number of alveolar CD8⁺ cells between the two groups (Figure 2B).

Even though no difference in the amount of cytotoxic CD8⁺ T cells was observed, there was a significant relationship between the quantity of GzmB⁺ cells in alveolar space and severity of airflow limitation.

Despite the advanced chronological age of the cohort (mean 68.3 ± 7.7 years), there was large variation on the severity of airflow limitation in these subjects (Figure 1A). It is a question what makes this difference. This study showed that lungs with higher alveolar GzmB⁺ cell contents

were associated with minimal or no airflow limitation, whereas those with lower alveolar GzmB⁺ cell contents were more likely to have airflow limitation (Figure 2A). These findings are also consistent with the previously reported finding of Treg cell upregulation in smokers without airflow limitation. Collectively, these results indicate that the relationship between GzmB⁺ cells and FEV₁ in CLE lungs is comparable to that observed between Treg cells in lung tissues or BAL fluid and FEV₁ in patients with COPD. Together, these data raise the possibility that GzmB⁺ cells may in part contribute to the pathogenesis of airflow limitation.

Granzyme B as an effector molecule of Treg cells

Treg cells employ multiple suppressive mechanisms, including cytokine secretion, metabolic control, and cell contact inhibition to restrain excessive immune activation to prevent autoimmunity.¹⁴ Target cell killing is a mechanism of Treg cell-mediated suppression through cell contact-dependent cytotoxicity of target cells, which is mediated by granzymes A (Gzma) and/or B (GzmB) in a perforin-dependent or -independent manner. The perforin-granzyme pathway is not only crucial for the function of NK (natural killer) and CD8⁺ T cells but can also be used by Treg cells to limit the activity of these cells. Thus, the granzyme B pathway appears to be one of the mechanisms through which Treg cells govern immunological responses.¹⁵

The connection between GzmB and the immunosuppressive effects of Treg cells was initially demonstrated by the frequent presence of GzmB⁺ Treg cells in malignant tumor lesions.¹⁶ Many studies have demonstrated that a high rate of tumor-infiltrating Treg cells in solid tumors is significantly associated with poor prognosis. Furthermore, high numbers of GzmB⁺ Treg cells

were negatively correlated with the occurrence of acute transplant-versus-host disease after hematopoietic stem cell transplantation, implying a regulatory influence on adaptive immunity.¹⁷

The immune response in wild-type and GzmB-deficient mice infected with Sendai virus has been characterized.¹⁸ Treg cells from wild-type mice expressed high levels of GzmB in response to infection, and the depletion of Treg cells resulted in an increase in the number of CD8⁺ T cells. These findings indicated that GzmB in the Treg cell plays a role in immune regulation during viral infections. It was found that selective depletion of Treg cells during acute respiratory syncytial virus (RSV) infection increased viral clearance and cell influx into the lungs of mice.¹⁹ Conversely, inflammation was reduced when Treg cell numbers are increased. Lung Treg cells expressed Gzm B. In addition to animal studies, increased GzmB expression in CD4⁺ T cells in the BAL fluid of children with severe RSV infections has been reported.²⁰

Nature of granzyme B positive cells in lung tissues of centrilobular emphysema

Granzyme B is important for the ability of CD8⁺ T cells to kill their targets. However, it has been reported that only recently activated CD8⁺ T cells are capable of GzmB production.²¹ In chronic infection or cancer, CD8⁺ T cells are exposed to persistent antigenic signals, which lead to T cell exhaustion²² and progressive loss of effector function with reduced production of perforin and GzmB.²³ In addition to T cell exhaustion, senescent T cells with defects in proliferation and effector functions accumulate with age²⁴ and showed lower levels of perforin and GzmB after stimulation.²⁵

These reports suggest that most of GzmB⁺ cells in the lungs of the aforementioned CLE subjects (mean age: 63.8±7.7 years) might not be CD8⁺ T cells. According to double

staining in the previous immunohistochemical staining study,¹² the majority of GzmB⁺ cells were not CD8 positive, and that of CD8⁺ cells were not GzmB positive, indicating that most of GzmB⁺ cells were not CD8⁺ cells. Furthermore, in the small airway walls of the majority of individual CLE subjects, the volume fraction of GzmB⁺ cells exceeds that of CD8⁺ cells (Figure 3B),¹² suggesting that most of these GzmB⁺ cells were other than CD8⁺ T cells.

Although *FOXP3* is the master control gene for CD4⁺ Treg cell, human FoxP3⁺ cells may not be homogeneous. In humans, low levels of FoxP3 expression in a significant number of activated, non-suppressive conventional T cells make it difficult to clearly identify a cell as a Treg cell based solely on FoxP3 positivity.²⁶⁻²⁸ However, present presentation of detection and quantitative analysis of Gzm B⁺ cells by immunohistochemical staining of CLE lung tissue may help to evaluate the significance of these functionally distinct cytotoxic cells in human tissues.²⁹

Although GzmB⁺ cells in the tissues of CLE lungs have not been directly identified as Treg cells, there is indirect evidence to support that they are Treg cells. GzmB expression is observed in CD8⁺ T cells, NK cells, CD4⁺ T helper cells, Treg cells, B cells, dendritic cells, macrophages, mast cells and basophils.³⁰ But with the exception of Treg and dendritic cells, all of these cells, CD8⁺ T cells,⁴ CD4⁺ T helper cells,³¹ NK cells,³² macrophages,³³ mast cells,³⁴ basophils³⁵ and B cells³⁶ have been reported to be increased, but not decreased in the lungs of COPD patients. In our study, however, the abundance of Gzm B⁺ cells in lung tissue decreased in cases with low air flow (Figure 2A). Thus, by inference and process of elimination, it is believed that these Gzm B⁺ cells in lung tissue represent Treg cells.

Granzyme B is considered a potential functional marker for Treg cells. It is hypothesized

that Gzm B⁺ cells in lung tissue may mitigate lung damage induced by tobacco smoke by suppressing cytolytic CD8⁺ T cells.³⁷ This finding suggests that the amount of GzmB⁺ cells in smokers' lungs may influence the rate of COPD progression, supporting the potential therapeutic use of granzyme B-producing immunosuppressive cells to prevent or slow disease progression in its early stages.⁶

Statins modulate regulatory T cells

Recent studies have reported that incubation of mouse splenic Treg cells with pitavastatin significantly increases GzmB secretion compared with untreated controls.³⁸ Additionally, the authors employed a mouse model of carbon tetrachloride (CCl₄)-induced liver fibrosis to assess in vivo effects. Compared with controls, statin treatment significantly reduced collagen deposition in the liver 4 weeks after CCl₄ intraperitoneal injections. Moreover, statin treatment increased GzmB secretion and Treg cell proliferation in analyses of liver immune cells. Furthermore, statin treatment significantly reduced CD8⁺ T-cell infiltration into the liver, likely due to enhanced cytolytic activity by Treg cells. These results suggest that statins may reduce liver fibrosis by increasing Treg cell cytolytic activity. This animal study is consistent with the previous human clinical data. Patients with chronic hepatitis C who underwent repeated liver biopsies over 3.5 years demonstrated a significant reduction in progression of fibrosis among statin users.³⁹ In a murine model of allergic inflammation of the airways, it was shown that atorvastatin treatment leads to a higher frequency and phenotypic changes in Treg cells, which may limit peribronchial inflammation.⁴⁰

Large randomized clinical trials have shown that statins are beneficial for prevention of

cardiovascular disease, contributing to their widespread use in clinical practice.⁴¹ In addition to their well-established lipid-lowering effects, statins possess multiple potentially advantageous properties, including immunoregulatory and anti-inflammatory properties, collectively referred to as pleiotropic effects.⁴² Substantial evidence supports statins' ability to stimulate Treg cell development and reduce inflammation.^{43,44} Lovastatin has been shown to increase Treg cell numbers, promote migration to inflammatory tissues, and enhance suppressive function by inducing the transcription factor FOXP3.⁴⁵ Therefore, modulation of Treg cells is considered one of the pleiotropic effects of statins.⁴²

Prior studies on the effects of statins in COPD

The immunoregulatory and anti-inflammatory pleiotropic effects of statins have prompted extensive research on their potential benefits in patients with COPD. However, clinical trial results have been inconsistent. Some studies reported no appreciable improvement in pulmonary function, exacerbation rates, or mortality. While retrospective studies suggested apparent benefit, prospective trials generally showed no clinical effects. Consequently, current COPD guidelines do not recommend statins as a therapeutic agent. The reasons for these discrepancies remain unclear, but may include the specific statin used, insufficient treatment duration to achieve measurable clinical outcomes, or subtherapeutic statin dosages for immunomodulatory effects.⁴⁶ Notably, no benefit to statin was observed in subgroups with severe COPD and no cardiovascular comorbidities.⁴⁷

Although statins share a common mode of action, they vary in their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy.⁴⁸ The class comprises both synthetic and

naturally occurring compounds derived from fungi. Characteristics such as lipophilicity or hydrophilicity, elimination half-life, and potency to lower low-density lipoprotein cholesterol differentiate individual statins. Regarding immunomodulatory effect, atorvastatin has been shown to increase Treg cell numbers in human peripheral blood mononuclear cells, whereas mevastatin and pravastatin do not.⁴⁹ In addition to increasing Treg cells, atorvastatin may suppress CD8+ T cell activation, potentially reducing inflammatory response.⁵⁰ In contrast, simvastatin may activate CD8+ T cell effector functions.⁵¹ These differences among statins may partially explain the variable outcomes observed in clinical trials. Statins have been shown to increase Treg cell concentrations; however, this effect may be associated with increased risk of certain cancers, particularly in older individuals.⁵² Additionally, statin-induced Treg cell expansion may be detrimental in various infectious diseases and neurodegenerative conditions. Consequently, statins may not improve outcomes in acute COPD exacerbation, which are often infection-related and not contribute to all-cause mortality. Observational studies examining statin use and COPD mortality are also subject to substantial bias, potentially leading to overestimation of protective effects.⁵³

Use of statins in COPD with early disease

Animal studies indicate that simvastatin administered from the first day of smoke exposure prevents emphysema and pulmonary hypertension,⁵⁴ and attenuates small airway remodeling.⁵⁵ When simvastatin treatment began after 3 months of smoking in guinea pigs, it reversed smoke-induced pulmonary hypertension and prevented emphysema, but failed to prevent small airway remodeling.⁵⁶ These results imply that therapies that work well in animal models might work in

biological early COPD patients, but this is impractical because clinically it is difficult to identify early COPD. As a result, statin use in people with comparatively early clinical disease would be reasonable. Late stage of COPD is characterized by persistent inflammation and irreversible structural changes, limiting the efficacy of therapeutic interventions.⁵⁷ Some participants in prior statin clinical trial for COPD had advanced airflow limitation, including severe disease.⁵⁸ The limited response seen in this study may be largely due to advanced stage of the disease, underscoring the potential significance of early intervention.

Effect of statins on small airways of COPD

Most of the distal airway cross-sectional area consists of small airways, which are bronchi with an internal diameter of less than 2 mm and lacking cartilage support. Early functional impairment of the small airways often precedes the appearance of clinical symptoms, abnormal lung function, or radiographic abnormalities.⁵⁹ In COPD, small airways exhibit significant remodeling, including overall thickening of the airway wall. This thickening results from epithelial changes, mucoid plugs, increased inflammatory cell density, smooth muscle hyperplasia, and fibrosis.^{60,61}

The effect of simvastatin on the fibrotic function of primary cultured human airway smooth muscle cells has been investigated.⁶² The findings indicate that simvastatin inhibits the production and secretion of extracellular matrix by human airway smooth muscle cells, demonstrating its potential to suppress fibrosis in airway diseases. In the large COPDGene study, computerized tomographic scans showed that patients with COPD taking statins had significantly larger small airway diameters than those not taking statins.⁶³ Although FEV₁ did

not change, a prospective study of patients with COPD treated with atorvastatin for 3 months demonstrated a significant increase in inspiratory capacity and a reduction in thoracic gas volume, suggesting improvement in dynamic hyperinflation.⁶⁴ These results support the hypothesis that statins may exert specific effects on small airways disease.⁶⁵

Future trial of statin in COPD with minimal airflow limitation

Prospective studies evaluating statins in patients with early-stage COPD are limited. To determine whether statins act as disease-modifying agent capable of preventing or slowing the progression of COPD in patients with minimal airflow limitation (FEV₁ approximately 75% predicted⁶⁶), a prospective randomized controlled trial is urgently needed.

Atorvastatin is particularly recommended because it is widely prescribed,⁶⁷ and has been shown to reduce CD8+ T cell activation. A low dose is preferable, as higher doses have been associated with a negative correlation with Treg cell frequency.⁶⁸ Higher atorvastatin concentrations may also alter Treg cell phenotype by reducing Foxp3 expression and inhibiting in vitro suppressive function.⁶⁹ The duration of statin use affects the positive effects of the medication, according to observational study conducted on newly diagnosed COPD.⁷⁰ Consequently, it is recommended that the trial be continued for a minimum of one year in order to attain the best results. Additionally, this trial would be applicable to COPD with airway wall thickening, but not for emphysema-dominant COPD without airway wall thickening.⁷¹

Conclusion

COPD smokers exhibit reduced Treg cell levels, whereas smokers without airflow limitation demonstrate higher levels. Treg cells may mitigate lung damage by suppressing cytolytic effector CD8⁺ T-cell activity, and FEV₁ has been shown to correlate with Treg cell levels.

Statins are known to enhance Treg cell activity. However, findings from earlier prospective clinical trials in COPD have been inconsistent. Notably, participants in prospective trials often had more advanced airflow limitation and shorter durations of statin exposure. The findings on animal study suggest that statin therapy may have disease-modifying potential when initiated in COPD with early disease. Prospective trials focusing on COPD with early disease are urgent to determine whether statins can prevent or slow disease progression. It would be the most effective way for finding a tool to prevent or slow the progression of COPD.

Acknowledgements

Author contributions: WDK conceptualized and drafted the manuscript. DDS contributed

to reviewing and editing the manuscript.

All authors approved the manuscript submitted for publication.

Declaration of interest

The authors declare no conflict of interest related to this review.

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Figure 1

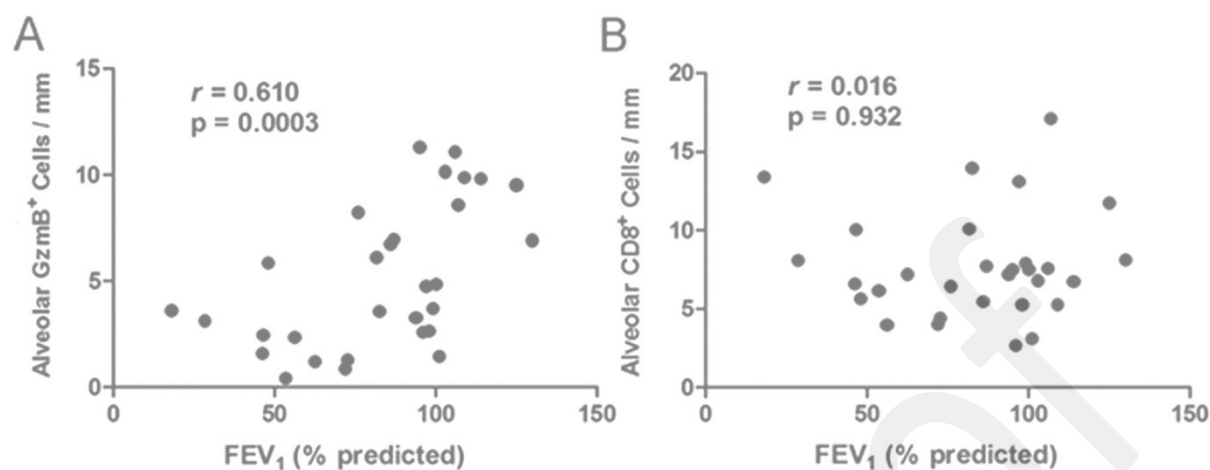


Figure 2

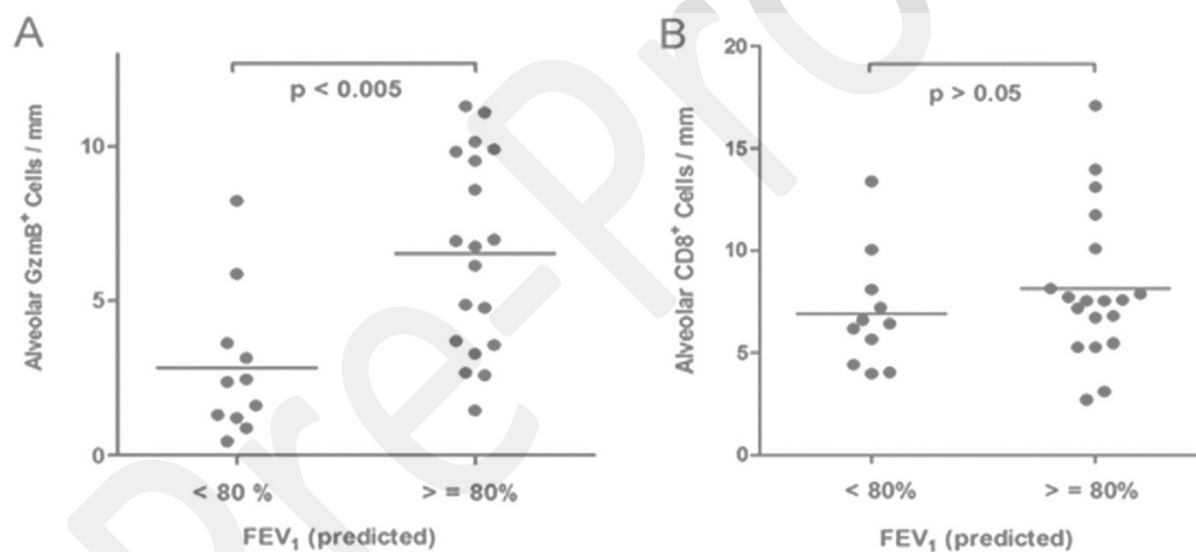


Figure 3

