Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Perspective

Statins as Regulatory T-Cell Modulators in COPD Early Disease

Won-Dong Kim, MD[1] Don D. Sin, MD[2]

Abstract

Early detection and intervention are critical to preventing or slowing the progression of chronic obstructive pulmonary disease (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 cluster of differentiation 8 (CD8+) T cells. Forced expiratory volume in 1 second (FEV_1) correlates with Treg cell levels in COPD. In lung tissue from surgically removed centrilobular emphysema lungs, granzyme (Gzm B)+ cells correlated with FEV_1. 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 humans. 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.

1. Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
2. Center for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

Abbreviations:

BAL=bronchoalveolar lavage; **CC14**=carbon tetrachloride; **CD8**=cluster of differentiation 8; **CLE**=centrilobular emphysema; **COPD**=chronic obstructive pulmonary disease; **FEV_1**=forced expiratory volume in 1 second; **FEV_1 %pred**= forced expiratory volume in 1 second percentage predicted; **FOXP3**=forkhead box P3; **Gzm B**=granzyme B; **NK**=natural killer; **PLE**=panlobular emphysema; **RSV**=respiratory syncytial virus; **Treg**=regulatory T cell

Funding Support:

None

Citation:

Kim WD, Sin DD. Statins as regulatory T-cell modulators in COPD early disease. *Chronic Obstr Pulm Dis.* 2026;13(6):529-537. doi: https://doi.org/10.15326/jcopdf.2026.0776

Publication Dates:

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

Address correspondence to:

Won-Dong Kim, MD
Department of Pulmonary and Critical Care Medicine
Asan Medical Center
University of Ulsan College of Medicine
Seoul, Republic of Korea
Phone: 82 10 8880 4491
Email: wdkim2@naver.com

Keywords:

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

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 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

For personal use only. Permission required for all other uses.

a faster annual decline in forced expiratory volume in 1 second (FEV_1) 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, is likely contributing to disease pathogenesis.[4] Patients with COPD have lower levels of regulatory T (Treg) cells in bronchoalveolar lavage (BAL) fluid than in smokers without COPD, 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, 9 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, 3 studies have demonstrated a significant association between Treg cell counts in the lung tissue or BAL fluid and FEV_1 percentage predicted (FEV_1 %pred).[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

In 2 studies, 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/mm^2 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 airways[12] were significantly correlated with FEV_1 %pred. Furthermore, lung tissue expression of GzmB, quantified by an enzyme-linked immunosorbent assay, was positively correlated with the FEV_1 %pred in smokers with FEV_1 <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 FEV_1 %pred was similar to previously reported correlations between the number of Treg cells in lung tissue or BAL fluid and FEV_1 %pred 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 FEV_1 ≥80% predicted than in those with FEV_1 <80% predicted (Figure 2A). Interestingly, however, in the same study, there was no difference in the number of alveolar CD8+ cells between the 2 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.

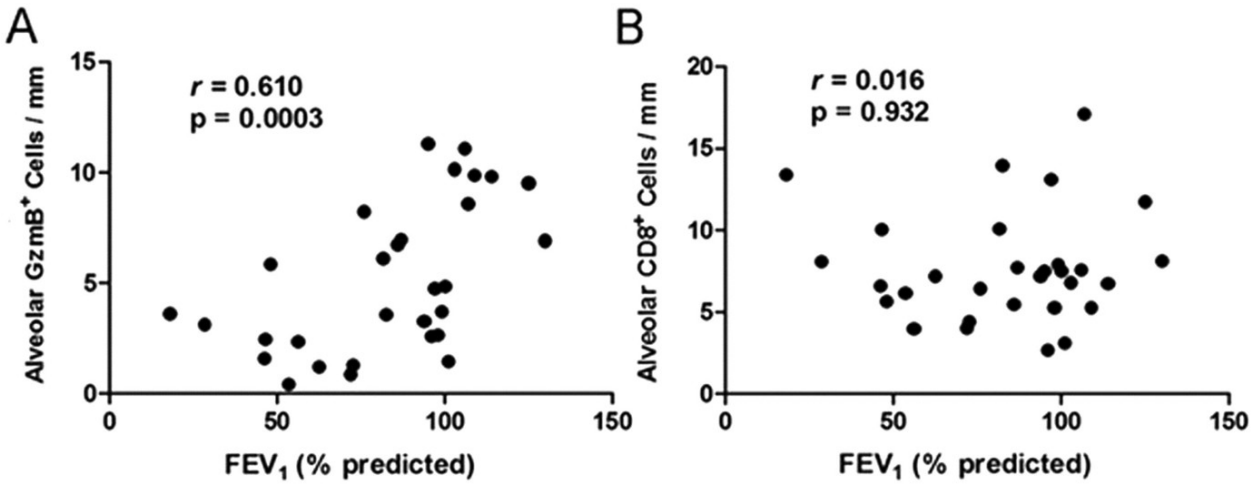
Despite the advanced chronological age of the cohort (mean 68.3±7.7 years), there was large variation on the severity of airflow limitation in these participants (Figure 1A). It is a question what makes this difference. This study showed that lungs with higher alveolar GzmB+ cell contents were associated 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 FEV_1 in CLE lungs is comparable to that observed between Treg cells in lung tissues or BAL fluid and FEV_1 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 Regulatory T 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-

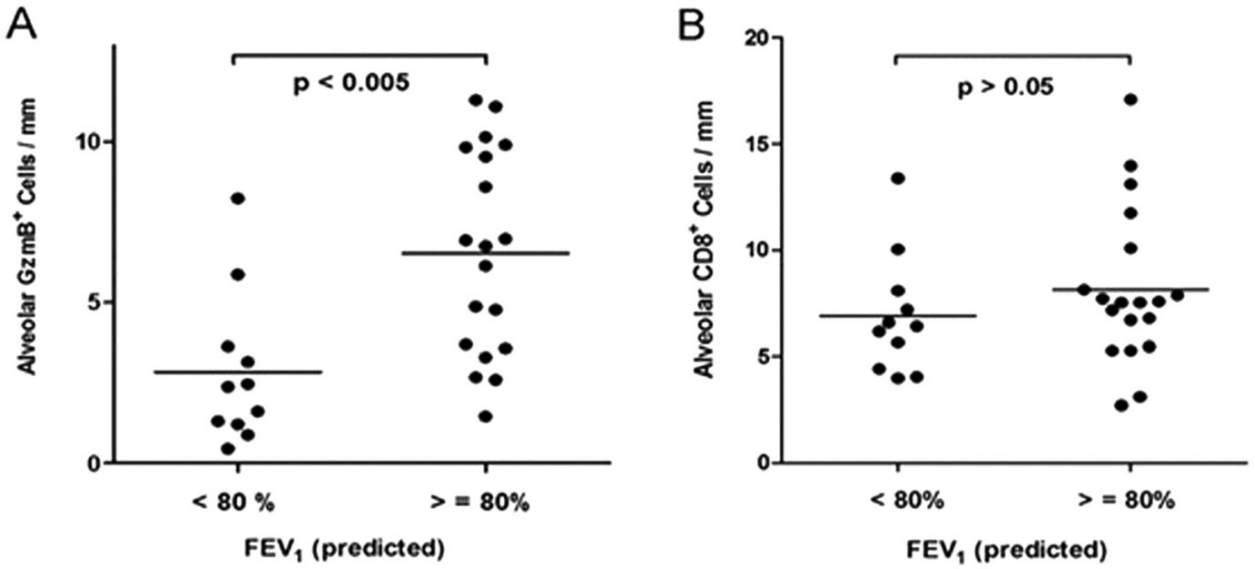
For personal use only. Permission required for all other uses.

Figure 1. The Relationship Between the Number of Alveolar Granzyme B+ Cells and Forced Expiratory Volume in 1 Second Predicted (A) and Between Alveolar Cluster of Differentiation 8+ Cells and Forced Expiratory Volume in 1 Second Predicted (B) in Participants With Centrilobular Emphysema[13]



Gzm B=granzyme B; FEV_1=forced expiratory volume in 1 second; CD8+=cluster of differentiation 8

Figure 2. Number of Granzyme B+ Cells (A) and Cluster of Differentiation 8+ Cells (B) in the Alveolar Walls of Participants With Centrilobular Emphysema With Forced Expiratory Volume in 1 Second Below 80% Predicted or With Forced Expiratory Volume in 1 Second 80% or More[13]



Gzm B=granzyme B; FEV_1=forced expiratory volume in 1 second; CD8+=cluster of differentiation 8

dependent cytolysis of target cells, which is mediated by granzymes A and/or GzmB in a perforin-dependent or -independent manner. The perforin-granzyme pathway is not only crucial for the function of natural killer (NK) and CD8+ T cells but can also be used by Treg cells to limit the activity of these cells. Thus, the GzmB 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

For personal use only. Permission required for all other uses.

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

GzmB 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 exhaustion[22] 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 age[24] 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 participants (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 participants, 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, nonsuppressive 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] basophils,[35] and B cells[36] have been reported to be increased, but not decreased in the lungs of COPD patients. In our study, however, the abundance of GzmB+ 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 GzmB+ cells in lung tissue represent Treg cells.

Granzyme B is considered a potential functional marker for Treg cells. It is hypothesized that GzmB+ 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 GzmB-producing immunosuppressive cells to prevent or slow disease progression in its early stages.[6]

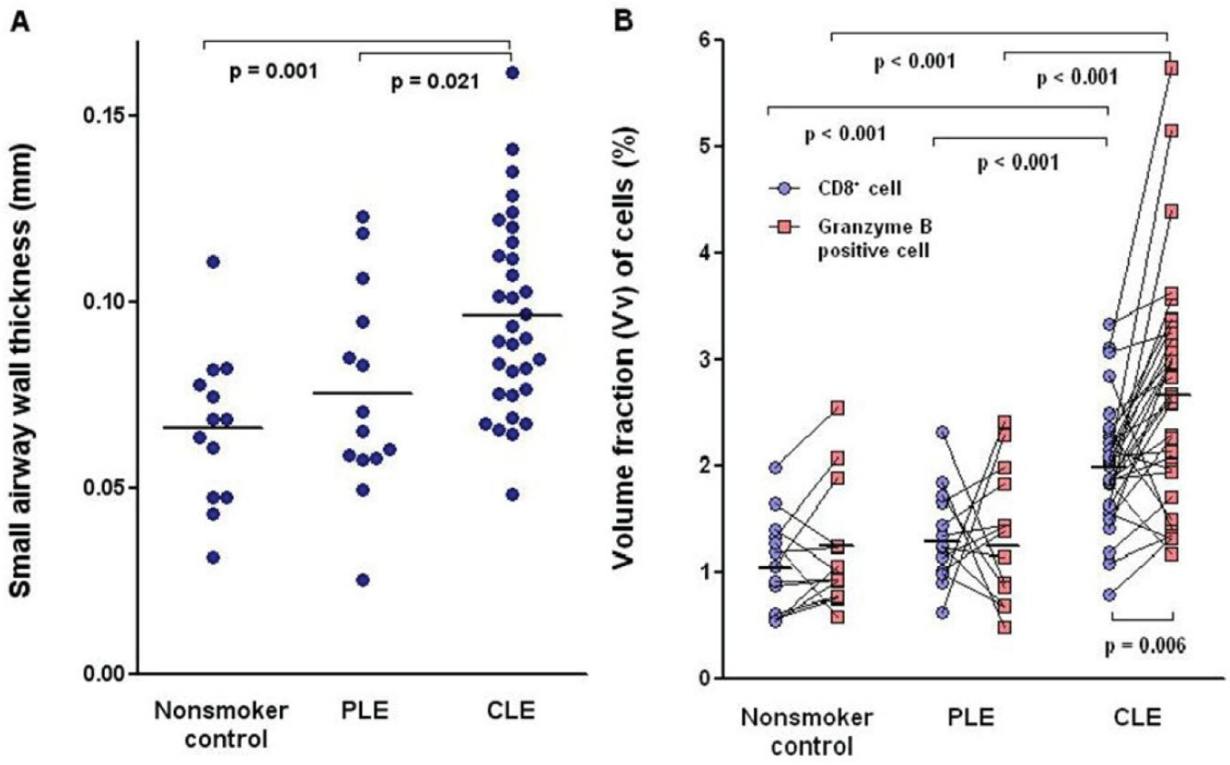
Statins Modulate Regulatory T Cells

A recent study 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]

For personal use only. Permission required for all other uses.

Figure 3. Small Airway Wall Thickness (A) and Volume Fraction of Cluster of Differentiation 8 and Granzyme B-Positive Cells (B) in Small Airway Walls of Nonsmoking Controls, Panlobular Emphysema, and Centrilobular Emphysema[12]



PLE=panlobular emphysema; CLE=centrilobular emphysema; CD8+=cluster of differentiation 8

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 do 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

For personal use only. Permission required for all other uses.

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 a 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 COPD Genetic Epidemiology (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 FEV_1 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 a disease-modifying agent capable of preventing or slowing the progression of COPD in patients with minimal airflow limitation (FEV_1 approximately 75% predicted),[66] 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 an 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 FEV_1 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 from animal studies 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 needed 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 manuscript.

For personal use only. Permission required for all other uses.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3(11):e442. https://doi.org/10.1371/journal.pmed.0030442

2. Agustí A, Faner R. COPD beyond smoking: new paradigm, novel opportunities. *Lancet Respir Med.* 2018;6(5):324-326. https://doi.org/10.1016/S2213-2600(18)30060-2

3. Bhatt SP, Soler X, Wang X, et al. Association between functional small airway disease and FEV_1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2016;194(2):178-184. https://doi.org/10.1164/rccm.201511-2219OC

4. Williams M, Todd I, Fairclough LC. The role of CD8+ T lymphocytes in chronic obstructive pulmonary disease: a systematic review. *Inflamm Res.* 2021;70:11-18. https://doi.org/10.1007/s00011-020-01408-z

5. Barceló B, Pons J, Ferrer JM, Sauleda J, Fuster A, Agusti AGN. Phenotypic characterization of T-lymphocytes in COPD: abnormal CD4+CD25+ regulatory T-lymphocyte response to tobacco smoking. *Eur Respir J.* 2008;31(3):555-562. https://doi.org/10.1183/09031936.00010407

6. Kim WD, Sin DD. Granzyme B may act as an effector molecule to control the inflammatory process in COPD. *COPD.* 2024;21(1):2299104. https://doi.org/10.1080/15412555.2023.2299104

7. Isajevs S, Taivans I, Strazda G, et al. Decreased FOXP3 expression in small airways of smokers with COPD. *Eur Respir J.* 2008;33(1):61-67. https://doi.org/10.1183/09031936.00145307

8. Chu S, Zhong X, Zhang J, Lao Q, He Z, Bai J. The expression of Foxp3 and ROR gamma t in lung tissues from normal smokers and chronic obstructive pulmonary disease patients. *Int Immunopharmacol.* 2011;11(11):1780-1788. https://doi.org/10.1016/j.intimp.2011.06.010

9. Hou J, Sun Y, Hao Y, et al. Imbalance between subpopulations of regulatory T cells in COPD. *Thorax.* 2013;68(12):1131-1139. https://doi.org/10.1136/thoraxjnl-2012-201956

10. Ström JE, Pourazar J, Linder R, et al. Airway regulatory T cells are decreased in COPD with a rapid decline in lung function. *Respir Res.* 2020;21:330. https://doi.org/10.1186/s12931-020-01593-9

11. Šileikiene V, Jurgauskien L. Role of regulatory T cells in pulmonary ageing and COPD development. *Int J Mol Sci.* 2025;26(8):3721. https://doi.org/10.3390/ijms26083721

12. Kim WD, Chi HS, Choe KH, et al. A possible role for CD8+ and non-CD8+ cell granzyme B in early small airway wall remodeling in centrilobular emphysema. *Respirology.* 2013;18(4):688-696. https://doi.org/10.1111/resp.12069

13. Kim WD, Chi HS, Choe KH, Kim WS, Hogg JC, Sin DD. The role of granzyme B containing cells in the progression of chronic obstructive pulmonary disease. *Tuberc Respir Dis (Seoul).* 2020;83(Supple 1):S25-S33. https://doi.org/10.4046/trd.2020.0089

14. Wang L, Liang Y, Zhao C, et al. Regulatory T cells in homeostasis and disease: molecular mechanisms and therapeutic potential. *Signal Transduct Target Ther.* 2025;10:345. https://doi.org/10.1038/s41392-025-02326-4

15. Gondek DC, Lu LF, Quezada SA, Sakaguchi S, Noelle RJ. Cutting edge: contact-mediated suppression by CD4+CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. *J Immunol.* 2005;174(4):1783-1786. https://doi.org/10.4049/jimmunol.174.4.1783

16. Wang W, Zou R, Qiu Y, et al. Interaction networks converging on immunosuppressive roles of granzyme B: special niches within the tumor microenvironment. *Front Immunol.* 2021;12:670324. https://doi.org/10.3389/fimmu.2021.670324

17. Drokov MY, Davydova JO, Kuzmina LA, et al. Level of Granzyme B-positive T-regulatory cells is a strong predictor biomarker of acute graft-versus-host disease after day +30 after allo-HSCT. *Leuk Res.* 2017;54:25-29. https://doi.org/10.1016/j.leukres.2017.01.014

18. Salti SM, Hammelev EM, Grewal JL, et al. Granzyme B regulates antiviral CD8+ T cell responses. *J Immunol.* 2011;187(12):6301-6309. https://doi.org/10.4049/jimmunol.1100891

19. Loebbermann J, Thornton H, Durant L, et al. Regulatory T cells expressing granzyme B play a critical role in controlling lung inflammation during acute viral infection. *Mucosal Immunol.* 2012;5(2):161-172. https://doi.org/10.1038/mi.2011.62

20. Bem RA, Bos AP, Bots M, et al. Activation of the granzyme pathway in children with severe respiratory syncytial virus infection. *Pediatr Res.* 2008;63:650-655. https://doi.org/10.1203/PDR.0b013e31816fdc32

21. Nowacki TM, Kuerten S, Zhang W, et al. Granzyme B production distinguishes recently activated CD8(+) memory cells from resting memory cells. *Cell Immunol.* 2007;247(1):36-48. https://doi.org/10.1016/j.cellimm.2007.07.004

22. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol.* 2015;15:486-499. https://doi.org/10.1038/nri3862

23. Iga N, Otsuka A, Yamamoto Y, et al. Accumulation of exhausted CD8+ T cells in extramammary Paget's disease. *PLoS One.* 2019;14(1):e0211135. https://doi.org/10.1371/journal.pone.0211135

24. Zhang J, He T, Xue L, Guo H. Senescent T cells: a potential biomarker and target for cancer therapy. *EBioMedicine.* 2021;68:103409. https://doi.org/10.1016/j.ebiom.2021.103409

25. Henson SM, Macaulay R, Riddell NE, Nunn CJ, Akbar AN. Blockade of PD-1 or p38 MAP kinase signaling enhances senescent human CD8(+) T-cell proliferation by distinct pathways. *Eur J Immunol.* 2015;45(5):1441-1451. https://doi.org/10.1002/eji.201445312

26. Wang J, Ioan-Facsinay A, van der Voort EIH, Huizinga TWJ, Toes REM. Transient expression of FOXP3 in human activated nonregulatory CD4+ T cells. *Eur J Immunol.* 2007;37(1):129-138. https://doi.org/10.1002/eji.200636435

For personal use only. Permission required for all other uses.

27. Miyara M, Yoshioka Y, Kitoh A, et al. Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor. *Immunity*. 2009;30(6):899-911. https://doi.org/10.1016/j.immuni.2009.03.019

28. Santosh Nirmala S, Kayani K, Gliwiński M, et al. Beyond FOXP3: a 20-year journey unravelling human regulatory T-cell heterogeneity. *Front Immunol*. 2024;14:1321228. https://doi.org/10.3389/fimmu.2023.1321228

29. Hameed A, Truong LD, Price V, Kruhenbuhl O, Tschopp J. Immunohistochemical localization of granzyme B antigen in cytotoxic cells in human tissues. *Am J Pathol*. 1991;138(5):1069-1075. https://pmc.ncbi.nlm.nih.gov/articles/PMC1886029/

30. Velotti F, Barchetta I, Cimini FA, Cavallo MG. Granzyme B in inflammatory diseases: apoptosis, inflammation, extracellular matrix remodeling, epithelial-to-mesenchymal transition and fibrosis. *Front Immunol*. 2020;11:587581. https://doi.org/10.3389/fimmu.2020.587581

31. Qin K, Xu B, Pang M, Wang H, Yu B. The functions of CD4 T-helper lymphocytes in chronic obstructive pulmonary disease. *Acta Biochim Biophys Sin (Shanghai)*. 2022;54(2):173-178. https://doi.org/10.3724/abbs.2021009

32. Rao Y, Le Y, Xiong J, Pei Y, Sun Y. NK Cells in the pathogenesis of chronic obstructive pulmonary disease. *Front Immunol*. 2021;12:666045. https://doi.org/10.3389/fimmu.2021.666045

33. Finicelli M, Digilio FA, Galderisi U, Peluso G. The emerging role of macrophages in chronic obstructive pulmonary disease: the potential impact of oxidative stress and extracellular vesicle on macrophage polarization and function. *Antioxidants (Basel)*. 2022;11(3):464. https://doi.org/10.3390/antiox11030464

34. Ballarin A, Bazzan E, Zenteno RH, et al. Mast cell infiltration discriminates between histopathological phenotypes of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(3):233-239. https://doi.org/10.1164/rccm.201112-2142OC

35. Jogdand P, Mori M, Bergqvist A, Walls A, Sanden C, Erjefalt J. Mapping of eosinophil and basophils in COPD lung tissues. *Eur Respir J*. 2015;46(suppl 59):PA384. https://doi.org/10.1183/13993003.congress-2015.PA384

36. Bosken CH, Hards J, Gatter K, Hogg JC. Characterization of the inflammatory reaction in the peripheral airways of cigarette smokers using immunocytochemistry. *Am Rev Respir Dis*. 1992;145(4 Pt 1):911-917. https://doi.org/10.1164/ajrccm/145.4_Pt_1.911

37. Robertson SJ, Messer RJ, Carmody AB, Hasenkrug KJ. In vitro suppression of CD8+ T cell function by Friend virus-induced regulatory T cells. *J Immunol*. 2006;176(6):3342-3349. https://doi.org/10.4049/jimmunol.176.6.3342

38. Bae AN, Lee H, Yang H, et al. Enhancing regulatory T cell function by mevalonate pathway inhibition prevents liver fibrosis. *Biochem Biophys Res Commun*. 2025;742:151094. https://doi.org/10.1016/j.bbrc.2024.151094

39. Simon TG, King LY, Zheng H, Chung RT. Statin use is associated with a reduced risk of fibrosis progression in chronic hepatitis C. *J Hepatol*. 2015;62(1):18-23. https://doi.org/10.1016/j.jhep.2014.08.013

40. Blanquiceth Y, Rodríguez-Perea AL, Tabares Guevara JH, et al. Increase of frequency and modulation of phenotype of regulatory T cells by atorvastatin is associated with decreased lung inflammatory cell infiltration in a murine model of acute allergic asthma. *Front Immunol*. 2016;7:620. https://doi.org/10.3389/fimmu.2016.00620

41. Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. *Curr Pharm Des*. 2012;18(11):1519-1530. https://doi.org/10.2174/138161212799504803

42. Shahbaza SK, Sadeghia M, Koushkia K, Penson PE, Sahebkar A. Regulatory T cells: possible mediators for the anti-inflammatory action of statins. *Pharmacol Res*. 2019:149:104469. https://doi.org/10.1016/j.phrs.2019.104469

43. Greca E, Kacimi O, Poudel S, et al. Immunomodulatory effect of different statin regimens on regulatory T-cells in patients with acute coronary syndrome: a systematic review and network meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Pharmacother*. 2023;9(2):122-128. https://doi.org/10.1093/ehjcvp/pvac047

44. Forero-Peña DA, Gutierrez FRS. Statins as modulators of regulatory T-cell biology. *Mediators Inflamm*. 2013;2013(1):167086. https://doi.org/10.1155/2013/167086

45. Mira E, León B, Barber DF, et al. Statins induce regulatory T cell recruitment via a CCL1 dependent pathway. *J Immunol*. 2008;181(5):3524-3534. https://doi.org/10.4049/jimmunol.181.5.3524

46. Carlson A, Smith E, Reid D. The stats are in: an update on statin use in COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10(1):2277-2284. https://doi.org/10.2147/COPD.S78875

47. Ingebrigtsen TS, Marott J/l, Nordestgaard BG, Lange P, Hallas J, Vestbo J. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. *Thorax*. 2015;70(1):33-40. https://doi.org/10.1136/thoraxjnl-2014-205795

48. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol*. 2005;19(1):117-125. https://doi.org/10.1111/j.1472-8206.2004.00299.x

49. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4+CD25+ T cells. *Atherosclerosis*. 2008;197(2):829-839. https://doi.org/10.1016/j.atherosclerosis.2007.07.031

50. Overton ET, Sterrett S, Westfall AO, et al. Effects of atorvastatin and pravastatin on immune activation and T-cell function in antiretroviral therapy-suppressed HIV-1 infected patients. *AIDS*. 2014;28(17):2627-2631. https://doi.org/10.1097/QAD.0000000000000475

For personal use only. Permission required for all other uses.

51. Yuan W, Ren X, Zhu J, et al. Single-intraosseous simvastatin injection suppresses cancers via activating CD8+ T cells. *Biomed Pharmacother*. 2022:155:113665. https://doi.org/10.1016/j.biopha.2022.113665

52. Goldstein MR, Mascitelli L, Pezzetta F. The double-edged sword of statin immunomodulation. *Int J Cardiol*. 2009;135(1):128-130. https://doi.org/10.1016/j.ijcard.2008.01.023

53. Sule NO, Suissa S. Statins and mortality in COPD: a methodological review of observational studies. *COPD*. 2023;20(1):284-291. https://doi.org/10.1080/15412555.2023.2242489

54. Lee JH, Lee DS, Kim EK, et al. Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. *Am J Respir Crit Care Med*. 2005;172(8):987-993. https://doi.org/10.1164/rccm.200501-041OC

55. Ou XM, Wen FQ, Uhal BD, et al. Simvastatin attenuates experimental small airway remodelling in rats. *Respirology*. 2009;14(5):734-745. https://doi.org/10.1111/j.1440-1843.2009.01549.x

56. Wright JL, Zhou S, Preobrazhenska O, et al. Statin reverses smoke-induced pulmonary hypertension and prevents emphysema but not airway remodeling. *Am J Respir Crit Care Med*. 2011;183(1):50-58. https://doi.org/10.1164/rccm.201003-0399OC

57. Churg A, Sin DD, Wright JL. Everything prevents emphysema: are animal models of cigarette smoke-induced chronic obstructive pulmonary disease any use? *Am J Respir Cell Mol Biol*. 2011;45(6):1111-1115. https://doi.org/10.1165/rcmb.2011-0087PS

58. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med*. 2014;370(23):2201-2210. https://doi.org/10.1056/NEJMoa1403086

59. Hogg JC, Paré PD, Hackett TL. The contribution of small airway obstruction to the pathogenesis of chronic obstructive pulmonary disease. *Physiol Rev*. 2017;97(2):529-552 https://doi.org/10.1152/physrev.00025.2015

60. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-2653. https://doi.org/10.1056/NEJMoa032158

61. Higham A, Quinn AM, Cançado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res*. 2019;20:49. https://doi.org/10.1186/s12931-019-1017-y

62. Schaafsma D, Dueck G, Ghavami S, et al. The mevalonate cascade as a target to suppress extracellular matrix synthesis by human airway smooth muscle. *Am J Respir Cell Mol Biol*. 2011;44(3):394-403. https://doi.org/10.1165/rcmb.2010-0052OC

63. Bercz PA, Kim V, Marchetti N, et al. Statin use in COPDGene subjects is associated with larger airways and fewer exacerbations. *Am J Respir Crit Care Med*. 2011;183(Supplement_1):A3111. https://academic.oup.com/ajrccm/article/183/Supplement_1/A3111/8617616

64. Mroz RM, Tycinska L, Minarowski L, er al. Pleiotropic effects of add-on atorvastatin therapy during the treatment of COPD patients. *Am J Respir Crit Care Med*. 2011;183(Supplement_1):A3106. https://academic.oup.com/ajrccm/article/183/Supplement_1/A3106/8618395

65. Young RP, Hopkins RJ. Statins and small airways disease in COPD. *Am J Respir Cell Mol Biol*. 2013;49(3):501. https://doi.org/10.1165/rcmb.2011-0422LE

66. Soriano JB, Polverino F, Cosio BG. What is early COPD and why is it important? *Eur Respir J*. 2018;52(6):1801448. https://doi.org/10.1183/13993003.01448-2018

67. Matyori A, Brown CP, Ali A, Sherbeny F. Statins utilization trends and expenditures in the U.S. before and after the implementation of the 2013 ACC/AHA guidelines. *Saudi Pharm J*. 2023;31(6):795-800. https://doi.org/10.1016/j.jsps.2023.04.002

68. Sorathia N, Al-Rubaye H, Zal B. The effect of statins on the functionality of CD4+CD25+FOXP3+ regulatory T-cells in acute coronary syndrome: a systematic review and meta-analysis of randomised controlled trials in Asian populations. *Eur Cardiol*. 2019;14(2):123-129. https://doi.org/10.15420/ecr.2019.9.2

69. Rodriguez-Perea AL, Rojas M, Velilla-Hernandez PA. High concentrations of atorvastatin reduce in-vitro function of conventional T and regulatory T cells. *Clin Exp Immunol*. 2019;196(2):237-248. https://doi.org/10.1111/cei.13260

70. Ajmera M, Shen C, Sambamoorthi U. Association between statin medications and COPD-specific outcomes: a real-world observational study. *Drugs Real World Outcomes*. 2017;4:9-19. https://doi.org/10.1007/s40801-016-0101-6

71. Kim WD. Phenotype of chronic obstructive pulmonary disease based on computed tomography-defined underlying pathology. *Tuberc Respir Dis (Seoul)*. 2022;85(4):302-312. https://doi.org/10.4046/trd.2022.0029

For personal use only. Permission required for all other uses.