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REVIEW

Autoimmune Pulmonary Alveolar Proteinosis: A Review of Pathogenesis and Emerging Therapies

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Abstract

Purpose of Review Autoimmune pulmonary alveolar proteinosis is a heterogenous clinical syndrome of disordered surfactant clearance due to a dysfunctional granulocyte–macrophage colony-stimulating factor signaling axis in the setting of polyclonal autoantibody generation. Recent advancements identifying key mechanistic drivers of this disease have been made. This clinical review summarizes current knowledge of autoimmune pulmonary alveolar proteinosis with an emphasis on contemporary findings on pathogenesis and emerging therapies.

Recent Findings A disturbed granulocyte–macrophage colony-stimulating factor signaling axis leads to downstream dysregulation of cholesterol export within alveolar macrophages. Accumulation of cholesterol impedes surfactant clearance and propagates the syndrome's disease process.

Summary Whole lung lavage therapy is an invasive procedure performed under general anesthesia which remains the standard of care for autoimmune pulmonary alveolar proteinosis. Augmentation of the defective signaling axis with recombinant human granulocyte-macrophage colony-stimulating factor is a promising treatment modality.

Keywords Alveolar macrophage · Alveolar macrophage lipidome · Autoimmune pulmonary alveolar proteinosis · Granulocyte–macrophage colony-stimulating factor · Pulmonary alveolar proteinosis · Pulmonary surfactant

Introduction

Pulmonary alveolar proteinosis (PAP) is a clinical syndrome of disordered surfactant homeostasis which leads to accumulation of surfactant-derived lipoproteinaceous material within the distal airspaces and results in impaired gas exchange and progressive respiratory compromise. The estimated prevalence of PAP is at least 7 cases per million individuals [1]. Due to its rarity and nonspecific phenotypic profile, the syndrome is commonly associated with diagnostic delay as well as a significant burden of comorbidity, healthcare utilization, and economic cost [2]. First identified in 1958, PAP is now recognized as a heterogenous spectrum of disorders characterized by defective surfactant clearance primarily due to a loss of a functional alveolar macrophage population [3]. The syndrome is classified into mechanistically distinct categories [4, 5•]. Primary PAP emerges due to disruption of granulocyte–macrophage colony-stimulating factor (GM-CSF) signaling secondary to an autoimmune pathology (i.e., GM-CSF autoantibodies) or inheritance of defective subunits of the GM-CSF receptor.

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Secondary PAP manifests from various underlying disease states (e.g., hematologic malignancies, immunodeficiency syndromes) leading to relative impairment of alveolar macrophages. Congenital PAP arises in conditions of dysregulated surfactant processing due to mutations in genes required for normal production. Of these types, autoimmune PAP accounts for over 90% of cases [6]. This clinical review summarizes current knowledge of autoimmune PAP with an emphasis on contemporary findings on pathogenesis and emerging therapies.

Pathogenesis

The primary mechanistic driver of PAP pathogenesis is a reduction of surfactant clearance. Pulmonary surfactant is a surface-active agent composed of phospholipids (80%, primarily dipalmitoylphosphatidylcholine), surfactant proteins (10%), and neutral lipids (10%, primarily cholesterol) [7]. Adsorption of pulmonary surfactant to the air–liquid interface functions to reduce surface tension and prevent end-expiratory alveolar collapse. Surfactant homeostasis is principally regulated by type II alveolar epithelial cells, which synthesize and secrete constituents of the surfactant layer on the alveolar surface. Pulmonary surfactant is then degraded or recycled within the lamellar structures of type II alveolar epithelial cells or by alveolar macrophages. Components of the degraded surfactant, including phospholipids and neutral lipids, are cleared via independent processing pathways.

GM-CSF is a 23 kDa glycoprotein produced by multiple cell types with a wide activity spectrum which exerts its biological effects through distinct intracellular signaling pathways [8]. The growth factor and immunomodulatory cytokine activates a cascade of transcription factor and effector protein functions to generate the proliferation, terminal differentiation, and activation of multiple cell types including matured myeloid cells (i.e., granulocytes, macrophages). Within the realm of PAP, crucial molecular discoveries have informed contemporary understanding of the syndrome's pathogenesis. Preserved GM-CSF signaling is required for terminal differentiation of pulmonary alveolar macrophages and critical processing and effector functions [8]. GM-CSF also regulates a crucial signaling axis that involves transcription factors purine-rich box1 (PU.1) and peroxisome proliferator-activated receptor gamma (PPAR-γ) [9]. PPAR-γ, a type II nuclear receptor, is a known regulator of adipogenesis and lipid metabolism. In a JAK2-mediated mechanism, PPAR-γ colocalizes with PU.1 and acts on target protein ATP binding cassette subfamily G member 1 (ABCG1), a regulator of intracellular sterol stores [10].

In pulmonary alveolar macrophages, the biological effects of the GM-CSF–PU.1–PPARγ–ABCG1 signaling axis is important with respect to the handling of cholesterol following surfactant degradation and clearance. GM-CSF has been shown to constitutively regulate the rate of cholesterol efflux and reverse transport within alveolar macrophages. Disruption of GM-CSF signaling results in impaired cholesterol export that is unsuccessfully ameliorated by alternative compensatory pathways including that of liver X receptor α (LXR- α), a key modulator of lipid and cholesterol homeostasis via target protein ATP binding cassette subfamily A member 1 (ABCA1) [11]. The excess sterol is esterified and stored in lipid droplets, producing "foamy macrophages" that progressively become engorged with insoluble material. Thus, the primary pathogenic insult of PAP is pathologic accumulation of cholesterol within pulmonary alveolar macrophages which secondarily impedes surfactant clearance and begets a dysfunctional surfactant layer with an elevated cholesterol:phospholipid ratio [12, 13].

In autoimmune PAP, disturbance of GM-CSF signaling is due to generation of polyclonal immunoglobulin G autoantibodies [12, 14]. These high affinity neutralizing autoantibodies quell GM-CSF bioactivity via binding to multiple exclusive target epitopes distributed throughout the molecule [15]. One study conducted GM-CSF epitope mapping of autoantibodies collected from the sera of 107 patients with autoimmune PAP [16]. Results showed that although target epitopes varied, amino acids residues 78 to 94 were consistently recognized – a segment noted to be part of an important functional domain of GM-CSF. Provoking agents for the unconstrained generation of GM-CSF autoantibodies have not been clearly identified. Inhalation of tobacco smoke or toxic substances (e.g., silica, titanium dioxide) has an association with autoimmune PAP, but the data is not robust [17]. Interestingly, low levels of GM-CSF autoantibodies have been detected in healthy subjects [18]. This finding has been ascribed to an innate supervisory mechanism which regulates cellular immunity and myeloid activity. Only when autoantibody production is deranged beyond a critical concentration threshold does the symptomatology of PAP manifest. Moreover, it is clear that the central pathogenic mechanism extends beyond a concentration-dependent autoantibody mediated targeting of GM-CSF molecules as serum autoantibody levels do not correlate with disease severity [19]. Lastly, interference of GM-CSF signaling in autoimmune PAP necessarily impairs the antimicrobial capacity of alveolar macrophages and compromises a spectrum of lymphocyte and neutrophil mediated defensive functions against intracellular pathogens, such as antigen presentation, cellular adhesion, and phagocytosis [20–23]. In combination with a thickened, defective surfactant layer secondary to an elevated cholesterol:phospholipid ratio, autoimmune PAP diminishes the integrity of respiratory function and oxygen delivery as well as confers an elevated risk of opportunistic infections.

Clinical Presentation

The median age of diagnosis of autoimmune PAP is in the forties to fifties and there is a slight predilection for the male sex as well as an elevated risk in tobacco smokers [1]. Patients demonstrate a significantly variable natural history with a clinical presentation ranging from indolent to critically emergent. Studies indicate that up to one-third of patients may be asymptomatic at the time of diagnosis, while the remaining individuals will generally report exertional dyspnea followed by non-productive cough [6, 24, 25]. A productive cough or constitutional symptoms of fever or weight loss are less common and often associated with infection by an underlying opportunistic agent (e.g., *Mycobacterium tuberculosis*, *Nocardia*, *Aspergillus*, *Cryptococcus*) [26, 27]. A detailed history of environmental and toxic exposures as well as a family history of malignancy should be obtained. Physical examination is often normal but there can be evidence of cyanosis or fine end-expiratory crackles. The latter finding may be particularly evident in cases of autoimmune PAP and pulmonary fibrosis, which may occur in up to 9% of patients and is theorized to be an end-stage evolution of ineffective GM-CSF signaling [28]. Interestingly, a study of GM-CSF knockout murine models also demonstrated evidence of hepatic micro- and macrovesicular steatosis and fibrosis, attributed to a maladaptive hepatopulmonary axis in the setting of deranged lipid homeostasis [29]. Another study of GM-CSF $^{-/-}$ mice with observable features of PAP has also exhibited distinct complex fertility defects [30]. The potential for and incidence of these findings in human subjects with autoimmune PAP has not yet been reported.

Diagnostic Evaluation

Radiographic imaging of the chest will most often demonstrate bilateral alveolar infiltrates in a perihilar and basilar distribution; however, atypical cases including asymmetric alveolar filling or multiple foci of fibrosis may be seen. High-resolution computed tomography can demonstrate variable intralobular lines and interlobular thickening against a background of diffuse ground-glass opacities, forming a polygonal pattern that has been termed "crazy paving" due to its resemblance with irregularly shaped paving stones (Fig. 1) [31]. However, the crazy paving pattern is not specific to PAP and has been described in numerous acute, subacute, and chronic disease processes. Pulmonary function testing is largely nondiagnostic but will most often show a decreased diffusing capacity for carbon monoxide (DLCO) with or without a restrictive ventilatory defect [32].

A patient with a clinical presentation and radiographic findings compatible with PAP should be evaluated for autoimmune PAP using serum GM-CSF autoantibody testing (Fig. 2). Quantification of serum GM-CSF autoantibodies by enzyme-linked immunosorbent assay is a validated diagnostic tool and, when above a pre-specified threshold value, is near 100% specific and sensitive for autoimmune PAP with immediate distinction from hereditary, secondary, and congenital etiologies [4, 33, 34••, 35]. Recently, an enzyme-linked immunosorbent assay developed for quantification of GM-CSF autoantibodies from a dried blood spot card using fingertip capillary sampling demonstrated similar reliability [36]. In instances of autoantibody concentrations near the threshold value, assessment of diminished or absent GM-CSF signaling via STAT5 phosphorylation or cell-surface CD11b stimulation index tests may be employed [37, 38]. Conditions in which intermediate levels of neutralizing GM-CSF autoantibodies have been detected, including isolated infection by *Cryptococcus* or *Nocardia* without clinically apparent autoimmune PAP; synthesizing the clinical presentation, radiologic findings, and signaling analyses can likely resolve these cases [39, 40]. A host of additional serum biomarkers for diagnosis and prognostication of autoimmune PAP are under active investigation, but their clinical utility has not yet been realized [41].

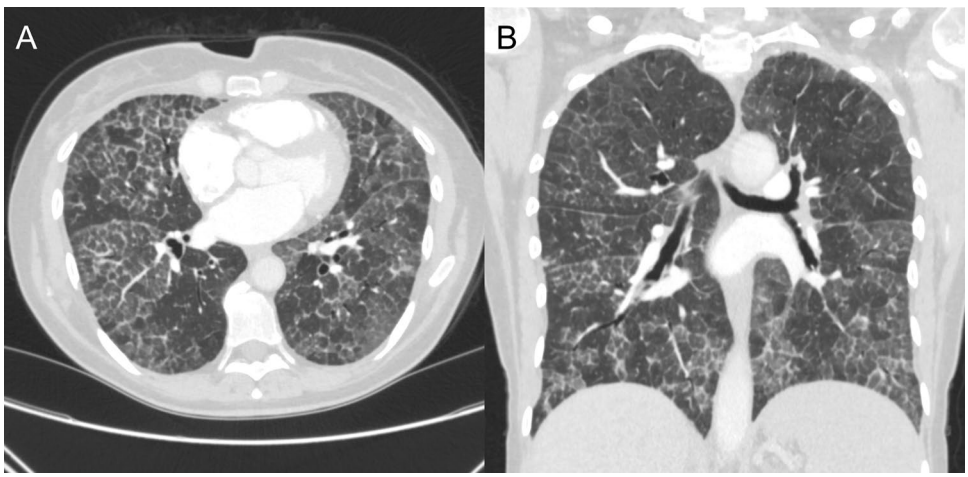

Fig. 1 High resolution computed tomography of the chest in axial (**A**) in coronal (**B**) view demonstrating bilateral diffuse ground-glass-airspace opacities with interlobular and intralobular septal thickening, termed a "crazy paving" pattern

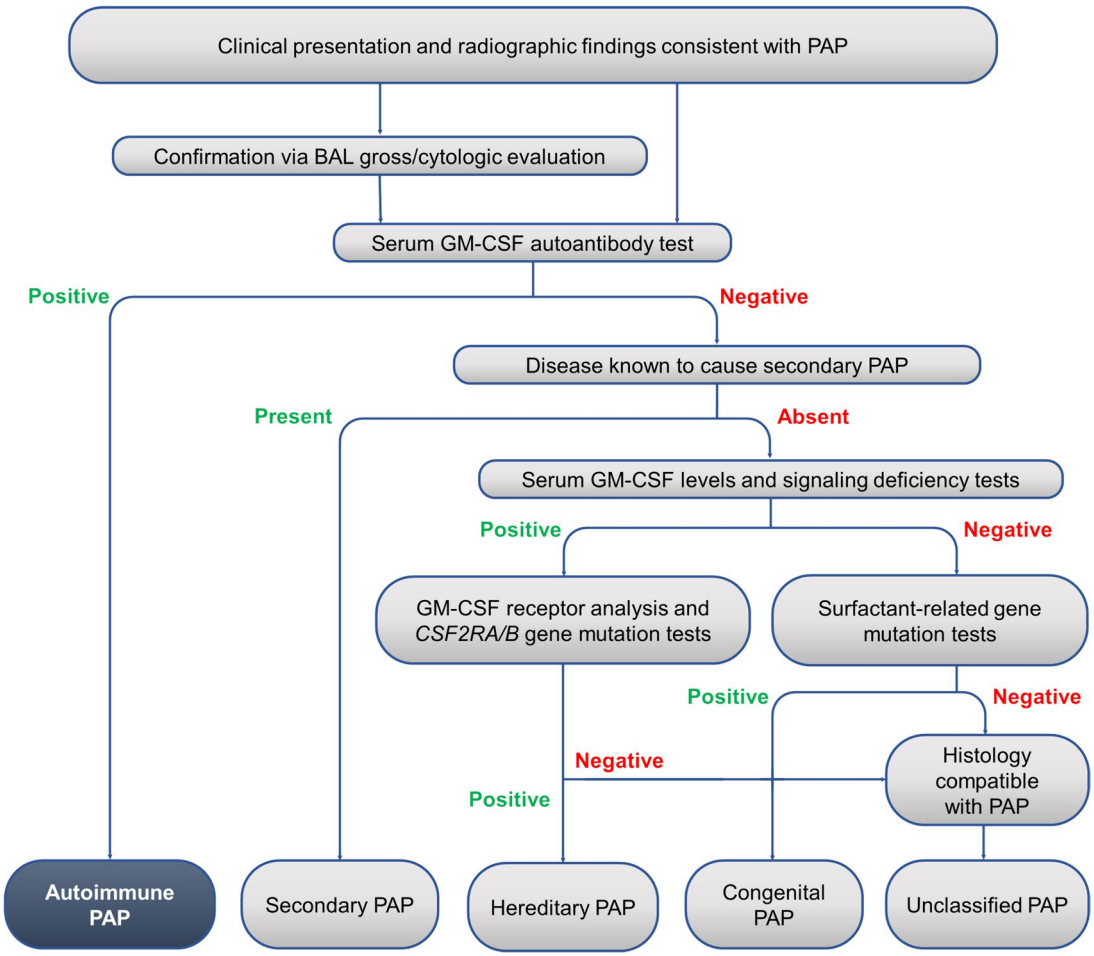

Fig. 2 Diagnostic algorithm for pulmonary alveolar proteinosis. A serum GM-CSF (granulocyte/macrophage colony–stimulating factor) autoantibody test is one of the principal tests to perform as it is highly sensitive and specific for diagnosis of autoimmune pulmonary alveolar proteinosis. In the event of a negative result, a combination of clinical history, additional serum testing, and mutational analysis will confirm alternate etiologies. Definition of abbreviations: BAL = bronchoalveolar lavage; GM-CSF = granulocyte–macrophage colony-stimulating factor; PAP = pulmonary alveolar proteinosis. Adapted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved. Cite: McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med 2022;205:1016–35.[5•] The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at [https://doi.org/10.1164/rccm.202112-2742SO]. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations

Patients with autoimmune PAP may often undergo flexible bronchoscopy with bronchoalveolar lavage. With the availability of GM-CSF autoantibody testing the need for bronchoscopy may not be necessary, however when bronchoalveolar lavage is performed the fluid return will appear opaque and milky. There will be lymphocyte-predominant cellularity and cytology exhibits foamy alveolar macrophages with periodic acid-Schiff-positive, diastase-resistant extracellular material. Stains and cultures for opportunistic infections should be obtained. Biopsy specimens are not often diagnostically necessary but would reveal periodic acid-Schiff-positive lipoproteinaceous material with surrounding foamy-appearing alveolar macrophages. Immunohistochemical staining can be positive for surfactant protein A.

Treatment and Outcomes

There are currently no curative therapies for autoimmune PAP. Standard of care is whole lung lavage; however, emerging pathogenesis-based therapies targeting the dysfunctional GM-CSF signaling axis are under active investigation.

Whole Lung Lavage

Whole lung lavage is a therapeutic intervention utilized in all etiologies of PAP to facilitate removal of accumulated pulmonary lipoproteinacious material [4, 5•, 12]. Common indications include activity-limiting dyspnea, a decline in lung function (i.e., DLCO, forced vital capacity), or observable radiologic progression [42]. Whole lung lavage is a procedure performed under general anesthesia in which a double lumen endotracheal tube is placed in a patient to ventilate the nontreated lung with 100% oxygen while the contralateral lung is lavaged with normal saline warmed to 37 °C. Although there is a wide degree of operator-dependent variability for the parameters of the procedure, the infusion–recovery cycle typically involves incremental instillation of 200–500 mL aliquots of saline after which chest percussion is performed to emulsify the sediment and the fluid is drained to gravity under a closed system. A total of 15–20 L of normal saline is generally administered of until the fluid return is clear. The initial effluent will be thick and milky with an observable sediment layer while terminal fluid returns clear with a reduced optical density. Remaining fluid may be aspirated with a flexible bronchoscope. Continuous intraoperative and post-operative monitoring of oxygenation status and lung function is recommended. The untreated, ventilated lung will typically be lavaged in a separate session. Patients may receive 2–3 treatments in a 5-year period. Many modifications to the procedure have been reported, including single session sequential bilateral lavage, lower infusion volume of 7 L saline, rapid infusion system as opposed to gravity drainage, concomitant veno-venous extracorporeal membrane oxygenation, manual or high-frequency percussive ventilation, and use of automated lung parenchymal pattern analysis of imaging data to quantify therapeutic response [43–49]. Complications are uncommon and include pneumothorax, pleural effusions, acute respiratory distress syndrome, saline spillover into the ventilated lung, and dilutional acidosis.

Although whole lung lavage has not been validated in randomized prospective trials, retrospective studies have emphasized therapeutic benefit. An early study evaluating treatment response to whole lung lavage reported treatment response in greater than 80% of patients with PAP for a median duration of 15 months [26]. Paired data indicated a significant primary improvement in partial pressure of oxygen (PaO2) with secondary benefit to Alveolar-arterial oxygen gradient (A-aDO_2), forced expiratory volume in 1 s, and vital capacity. Similar post-treatment trends in lung function data as well as improvement of symptoms, functional status and radiographic findings have been observed in a meta-analysis of 12 studies involving 206 patients with PAP and other contemporary investigations [50–53]. A recent retrospective analysis of 276 patients with PAP included 20 patients (14 with primary and 6 with secondary etiology, respectively) who underwent whole lung lavage. Two multivariate models demonstrated significant survival benefit in individuals who received whole lung lavage within 3 months of diagnosis (hazard ratio 0.12 [0.02—0.88] and 0.11 [0.02—0.85] for models 1 and 2, respectively) [53]. This is consistent with a review of literature asserting superior 5-year survival in patients who receive whole lung lavage compared to those who do not ($94 \pm 2\%$ vs. $85 \pm 5\%$, $p = 0.04$) [26]. A finding of hemoptysis prior to whole lung lavage has been associated with treatment failure [52].

GM-CSF Augmentation

In 1996, subcutaneous recombinant GM-CSF therapy was administered to one individual with PAP who had exhibited only brief periods of clinical benefit to whole lung lavage therapy, with results demonstrating enhanced functional capacity and A-aDO_2.[54] These findings stimulated interest in augmentation of the dysfunctional signaling axis in primary PAP using recombinant GM-CSF therapy (Table 1). Early studies of subcutaneous recombinant GM-CSF in patients with PAP demonstrated a response rate of 43–75% [55–57]. Primary endpoints generally included a narrowed A-aDO_2; improved symptom scores, PaO2, spirometric data, DLCO, and radiographic findings were also variably observed [55–59]. A subset of patients demonstrated cessation of supplemental oxygen requirements and reduced frequency of whole lung lavage therapy. Treatment response varied but lasted up to 3 years. Notably, clinical improvement was often not observed until 6 to 12 weeks of subcutaneous recombinant GM-CSF administration, which may reflect the time for therapeutic levels to overcome neutralizing autoantibodies as well as for successful terminal differentiation of progenitor cells. Treatment-related eosinophilia was predictive of therapy response, but this was not consistent across studies, which may be due to heterogenous hematopoietic stimulation from exogenous GM-CSF [56]. Adverse events most often included local erythema or injection-site edema, headache, and dyspnea. Neutropenia and asymptomatic splenomegaly were rarely reported.

Following positive results of an initial case in 2004, the use of aerosolized recombinant GM-CSF therapy subsequently became an attractive treatment modality for PAP [60]. Studies of nebulized sargramostim and molgramostim have ranged from retrospective observational investigations to larger randomized controlled clinical trials [61–70, 71••, 72]. A 2010 large multicenter, self-controlled, phase II trial investigated outcomes of a pre-specified regimen (high-dose followed by maintenance low-dose therapy) of aerosolized GM-CSF in 39 patients with autoimmune PAP, of whom 35 successfully

Table 1 Selected Studies of Granulocyte–Macrophage Colony–Stimulating Factor Augmentation Therapy in the Literature

Study	Year	Trial Design	*N*	Drug	Regimen	Findings
Subcutaneous						
Kavuru et al. [55]	2000	Phase I/II, single-site, open label	4	SGM	250 μg/d (mo 1) → 5 μg/kg/d (mo 2) → 7 to 9 μg/kg/d (mo 3)	75% response; improved symptom scores, PaO2, A-aDO_2, spirometric data, DLCO, and radiographic findings
Seymour et al. [56]	2001	Phase I/II, single-site, open label	14	MGM SGM	3 μg/kg/d (d 1–5) → 5 μg/kg/d (d 6-onwards) → escalate to max 20 μg/kg/d for 1–2 mo	43% response; improved A-aDO_2, DLCO, and radiographic findings, 6MWD; no change to spirometric data
Venkateshiah et al. [57]	2006	Phase I/II, single-site, open label	25	SGM	250 μg/d (mo 1) → 5 μg/kg/d (mo 2) → 9 μg/kg/d (mo 3) → escalate to max 18 μg/kg/d for 3–12 mo	48% response; improved PaO2, A-aDO_2, spirometric data, DLCO, radiographic findings, and 6MWD
Khan et al. [58]	2012	Retrospective, observational	4	NR	5 μg/kg/d for 3 mo; 3 patients with concomitant WLL	Improved radiographic findings and functional capacity
Hadda et al. [59]	2016	Retrospective, observational	3	NR	3–5 μg/kg/d for 6 wk; all patients with concomitant WLL	Improved radiographic findings and functional capacity
Zhang et al. [75]	2020	Phase I/II, single-site, open label	20	NR	75 μg/d for 3 mo → escalate to 150 μg/d for mo 2–3; followed by alternating d for an additional 3 mo	85% response; improved PaO2, A-aDO_2, spirometric data, DLCO, radiographic findings, and 6MWD
Inhaled						
Tazawa et al. [61]	2005	Phase I/II, single-site, open label	3	MGM	125 μg BID alternating wk for 6 mo	Improved A-aDO_2; reduced serum LDH/SP-D/CEA, BAL anti–GM-CSF antibodies and BAL immune complexes
Wylam [62]	2006	Retrospective, observational	12	SGM	250 μg BID alternating wk → escalate to 500 μg for 8 mo	92% response; improved PaO2, A-aDO_2, spirometric data, DLCO, and radiographic findings
Tazawa et al. [63]	2010	Phase I/II, multi-site, open label	39	SGM	250 μg/d (d 1–8; none d 9–14) for 3 mo → 125 μg/d (d 1–4; none d 5–14) for 3 mo	62% response; improved PaO2, A-aDO_2, spirometric data, DLCO, radiographic findings, and 6MWD
Ohashi et al. [64]	2012	Retrospective analysis (3 studies)	19	SGM	125–250 μg/d (regimen varied in pilot, early phase II, and multicenter phase II studies)	53% response in BAL analysis; reduced BAL total protein and SP-A; increased BAL CA-125 and IL-17
Papiris et al. [65]	2014	Retrospective, observational	6	SGM	250 μg/d (4 d on/4 d off) indefinitely; remission: reduce; relapse: escalate	100% fulfilled remission criteria by 25.6 ± 10 mo; improved symptom scores, PaO2, A-aDO_2, and DLCO
Campo et al. [66]	2016	Phase II, multi-site, open label	18	SGM	WLL (group A) vs. WLL → 250 μg/d alternating wk for 3 mo → 250 μg/d (2 d every 2 wk) for 6 mo (group B)	Improved spirometric data and DLCO in group B; reduced serum biomarkers
Ohkouchi et al. [67]	2017	Retrospective, observational	5	SGM	125 μg BID (d 1–8; none d 9–14) for 3 mo → 125 μg BID (d 1–4; none d 5–14) for 3 mo	Improved PaO2 and radiographic findings and reduced serum biomarkers only after WLL
Tazawa et al. [68]	2019	Phase III, multi-site, double-blind, RCT	64	SGM	125 μg BID alternating wk for 6 mo vs. placebo	Improved PaO2, A-aDO_2, DLCO, and radiographic findings; no change to 6MWD
Zhen et al. [69]	2020	Retrospective, observational	33	MGM	WLL (group A) vs. WLL → 150 μg BID alternating wk for 3 mo (group B)	Improved PaO2, A-aDO2, spirometric data, and recurrence rate in group B

Table 1 (continued)

Study	Year	Trial Design	*N*	Drug	Regimen	Findings
Tian et al. [70]	2020	Phase II, multi-site, open label	36	MGM	150 µg BID alternating wk for 3 mo → 150 µg/d alternating wk for 3 mo vs. placebo	Improved symptom scores, spirometric data, and DLCO; no change to A-aDO_2
Trapnell et al. [71••]	2020	Phase II, multi-site, double-blind RCT	138	MGM	300 µg/d either continuously or alternating wk vs. placebo for 6 mo	Improved symptom scores, PaO2, A-aDO_2, DLCO, and radiographic findings, especially in continuous therapy
Livingstone et al. [72]	2022	Retrospective, observational	5	SGM	125 µg BID alternating wk for 3 mo → 125 µg/d (d 1–4; none d 5–14) for 3 mo	Improved symptom scores, radiographic findings, and 6MWD; reduced respiratory-related hospitalizations
Campo et al. [77]	2024	Phase II, singe-site, open-label	18	SGM	WLL (group A) vs. WLL → 250 µg/d alternating wk for 3 mo → 250 µg/d (d 1, 3 every 14) for 6 mo (group B)	Longer time to first rescue WLL; improved PaO2, A-aDO_2, DLCO, and serum biomarkers in group B

Response rates and findings are reported as detailed; authors defer differentiation of intention-to-treat and per-protocol analysis to individual studies

Definition of abbreviations: *A-aDO*$_2$ Alveolar-arterial oxygen gradient, *BAL* bronchoalveolar lavage, *BID* two times per day, *DLCO* diffusing capacity for carbon monoxide, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *NR* not reported, *PaO2* partial pressure of oxygen in the arterial blood, *RCT* randomized controlled trial, *WLL* whole lung lavage, *6MWD* 6-min walk distance, *MGM* molgramostim, *SGM* sargramostim, *D* day, *MO* month, *WK* week

completed treatment [63]. There was a 62% response rate with significant improvement in the primary endpoint of A-aDO_2. A 30-month follow-up of these 35 patients demonstrated that 23 (66%) had no symptomatic recurrence while remaining individuals received additional inhaled treatments [73]. Notably, a low baseline vital capacity was significantly associated with disease recurrence. A 2019 double-blind, placebo-controlled trial investigated clinical outcomes of inhaled sargramostim in 64 patients with autoimmune PAP [68]. Exclusion criteria included those with whole lung lavage therapy within 6 months of the trial, previous use of GM-CSF or other cytokine therapy, or severe respiratory compromise during the enrollment period (PaO2 < 50 mmHg while breathing ambient air). Laboratory parameters, including PaO2, A-aDO_2, and serum biomarkers, significantly improved in the treatment group; however, clinical endpoints such as symptom assessment scores and 6-min walk distances (6MWD) did not differ. Interestingly, anti-GM-CSF antibody levels were greater in the treatment group with no changes in neutralizing capacity. The authors suggested inhaled therapy may accelerate their production. A 2020 placebo-controlled phase II randomized study evaluating outcomes in 36 patients after 6 months of inhaled molgramostim similarly noted modestly improved laboratory parameters with no significant clinical changes [70]. Another 2020 double-blind, placebo-controlled trial of 138 patients with autoimmune PAP included 2 treatment arms of continuous (daily) or intermittent (alternating weeks) inhaled molgramostim [71••]. Continuous therapy not only resulted in improvement across multiple endpoints, but also demonstrated enhanced clinical benefit (e.g., A-aDO_2, symptom scores) when compared to the intermittent treatment arm.

A 2018 meta-analysis of 10 available observational studies including 115 patients with autoimmune PAP compared the therapeutic efficacy of subcutaneous and inhaled GM-CSF [74]. Results indicated that, compared to subcutaneous GM-CSF, inhaled therapy was associated with a significantly higher pooled response rate (89% vs. 71%; $p = 0.023$) including greater improvement in PaO2 (21.02 mmHg vs. 8.28; $p < 0.01$) and reduction in A-aDO_2 (19.63 mmHg vs. 9.15 mmHg; $p < 0.01$). Pooled disease recurrence rate was not significantly different between treatment modalities (19% vs. 24%; $p = 0.262$). Subsequently, a 2020 phase I/II single-site open label study reported results of 6 months of subcutaneous GM-CSF therapy in 20 patients [75]. Treatment response was 85% (17 of 20 patients) and 83% (14 of 17 patients) at 6-month and 12-month follow-ups, respectively. There was significant post-treatment improvement in PaO2, A-aDO_2, forced vital capacity, DLCO, radiographic findings, and 6MWD at 6-month follow-up; compared to pre-treatment baselines, all parameters remained significantly improved at 12-month follow-up except A-aDO_2 and forced vital capacity. A subsequent 2023 systematic review and

meta-analysis examined 6 existing studies of 288 participants who received nebulized recombinant human GM-CSF [76]. Pooled results comparing treatment and control groups revealed improvements in symptom (St. George's Respiratory Questionnaire) scores (mean difference 8.09; $p < 0.01$), A-aDO_2 (mean reduction 4.36 mmHg; $p < 0.01$), and DLCO (mean increase 5.09% of predicted; $p < 0.01$). There was no significant change in 6MWD (mean increase 21.72 m; $p = 0.08$). No significant adverse events were reported in studies of inhaled GM-CSF. Recently, a 2024 randomized single-site phase II study investigated clinical outcomes of inhaled sargramostim in 18 patients with moderate-to-severe autoimmune PAP [77]. All patients received a baseline whole lung lavage during enrollment into the study. Patients were randomized in a 1:1 ratio to receive inhaled sargramostim (3 months of high-dose therapy followed by 6 months of low-dose therapy) or no scheduled therapy (control group). The primary endpoint of time until the first rescue whole lung lavage was significantly longer in the treatment group (30 vs. 18 months; $p < 0.01$), with an associated sevenfold increase in relative risk for requiring rescue whole lung lavage in the control group. Secondary endpoints of PaO2, A-aDO_2, DLCO, and serum biomarkers were also significantly improved in the treatment group. This study suggests that inhaled GM-CSF therapy may be more effective after a whole lung lavage. Currently, the phase 3 IMPALA-2 trial, a double-blinded, randomized, international study investigating daily inhaled molgramostim 300mcg versus placebo, just completed enrollment with anticipated results later this year [NCT02702180].

Summarily, GM-CSF augmentation with recombinant human GM-CSF therapy is a well-tolerated treatment and appears to be effective for patients with autoimmune PAP. A combination of whole lung lavage to deplete the accumulated surfactant burden with inhaled GM-CSF therapy to restore alveolar macrophage bioactivity may also be a promising treatment regimen. Optimal dosing has not yet been elucidated and is likely variably dependent on patients' individual accumulated surfactant and autoantibody levels.

Lipid Homeostasis

Following recognition of the dysfunctional GM-CSF–PU.1–PPARγ–ABCG1 signaling axis which results in defective alveolar macrophage cholesterol export, the alveolar lipidome became an increasingly attractive therapeutic target (Table 2) [78]. In fact, PAP may be associated with systemically dysregulated lipid homeostasis. When compared to 130 healthy adults, an analysis of fasting blood samples in 122 patients with PAP (116 with autoimmune etiology) revealed significantly higher levels of triglycerides, total cholesterol:high-density lipoprotein cholesterol ratio, triglyceride:high-density lipoprotein cholesterol ratio, and non-high-density lipoprotein cholesterol as well as lower levels of high-density lipoprotein cholesterol [79]. Total cholesterol:high-density lipoprotein cholesterol ratio and non-high-density lipoprotein cholesterol were also independent risk factors for severity of PAP. One study performed a quantitative lipidomic analysis of lipids and surfactant proteins in bronchoalveolar lavage samples from 34 patients with PAP (14 with autoimmune PAP) [80]. Results showed that, compared to healthy control subjects, the total lipid concentration of the alveolar fluid was increased up to 59-fold, suggesting that this expanded lipid pool could impede gas exchange. Furthermore, the concentration of free cholesterol was increased by 60-fold and cholesteryl esters by 24-fold. Concentration of ceramide and other sphingolipids was increased by more than 130-fold; these species have been associated with a proapoptotic microenvironment. Importantly, the free cholesterol:phospholipid ratio was elevated by twofold compared to healthy control subjects, which may be more pathogenically relevant than absolute elevations of concentration of lipid constituents within the alveolar surfactant system. These findings did not significantly differ by the mechanistically distinct etiologies of PAP and offered insight into targetable pathways for PAP.

The rise in the free cholesterol content of the alveolar macrophage lipid profile encouraged the clinical potential of statin therapy. A 2018 case study presented a patient with severe autoimmune PAP who demonstrated only transient improvement following multiple whole lung lavage treatments [13]. After 6 months of oral statin therapy, the patient exhibited remarkable improvement of dyspnea, oxygen requirements, radiographic disease severity, forced vital capacity, and DLCO. A similar response was seen in a second patient after 1 year of statin therapy. In a follow-up analysis, foamy alveolar macrophages derived from a patient with PAP were exposed to statin therapy ex vivo for 24 h. Lipid analysis revealed a 40% reduction in cholesterol content compared to control cells. Interestingly, mRNA transcript levels for ABCG1 and ABCA1 transporter proteins were elevated, revealing the mechanistic driver of clinical response to statin therapy. Positive treatment response to statin therapy was similarly seen in case studies of patients with PAP with or without dyslipidemia [81, 82]. Prospective observational studies of 40 and 50 patients with PAP treated with atorvastatin demonstrated at least a 65% response rate with improved PaO2 and DLCO as well as radiographic findings via quantitative analysis of high-resolution computed tomography scans [83, 84]. A higher baseline total cholesterol:high-density lipoprotein cholesterol ratio was associated with treatment response.

Because PAP is associated with abnormal alveolar macrophage expression of PPARγ and ABCG1 as well

Table 2 Selected Studies of Lipid-Targeting and Immunomodulatory Therapies in the Literature

Study	Year	Trial Design	*N*	Drug	Findings
Lipid homeostasis					
McCarthy et al. [13]	2018	Case study	2	Rosuvastatin	Improved symptoms, oxygen requirements, spirometric data, DLCO, and radiographic findings after 6 mo in patient 1; improved symptoms, DLCO, and radiographic findings after 12 mo in patient 2
Shi et al. [81]	2021	Case study	1	Atorvastatin	Improved symptoms, spirometric data, and radiographic findings after 18 mo in patient without hypercholesterolemia and unclassified PAP with poor response to prior WLL and inhaled GM-CSF treatments
Takano et al. [82]	2022	Case study	1	Rosuvastatin	Stable symptoms and radiographic findings without need for lung lavage therapy after 10 mo in patient with autoimmune PAP and dyslipidemia
Shi et al. [83]	2022	Prospective, observational	40	Atorvastatin	65% response in patients without hypercholesterolemia after 12 mo; 4 patients with complete response and 22 with partial response, including improved PaO2, DLCO, radiographic findings; no change to A-aDO2
Shi et al. [84]	2022	Prospective, observational	50	Atorvastatin	Improved radiographic findings via quantitative analysis of HRCT scans after 12 mo; decreased total lung opacification was correlated with improved PaO2 and DLCO, but not spirometric data
Dupin et al. [86]	2020	Case study	1	Pioglitazone	Modestly improved dyspnea, PaO2, spirometric data, DLCO, and radiographic findings after 12 mo of therapy (30 mg/d) with prior failed responses to WLL, inhaled/subcutaneous GM-CSF, and rituximab
Vis et al. [87]	2020	Case study	1	Pioglitazone	Clinical stability without improvement or deterioration in patient with autoimmune PAP after 9 mo of therapy (30 mg/d) with prior failed responses to WLL) and progressive fibrosis
Lee et al. [88]	2024	Retrospective, observational	8	Varied	Improved AM lipid content in patient 1 after 10 mo of inhaled GM-CSF and patient 3 after statin, pioglitazone, and inhaled GM-CSF for at least 12 mo (prior subcutaneous GM-CSF, rituximab, plasmapheresis)
Immunomodulation					
Akasaka et al. [91]	2015	Retrospective, observational	31	Prednisolone	Overall cumulative worsening rate of 80.8% during steroid therapy; significantly higher worsening rate with elevated prednisolone dosages; increased risk of infection following steroid treatment
Borie et al. [95]	2009	Case study	1	Rituximab	Treatment (1000 mg IV on d 1 and 15) resulted in improved dyspnea, A-aDO_2, spirometric data, DLCO, radiographic findings, and 6MWD after 12 mo; reduced serum anti-GM-CSF IgG and neutralizing activity
Amital et al. [96]	2010	Case study	1	Rituximab	Patient with only partial remission with WLL and subcutaneous GM-CSF demonstrated improved PaO2, DLCO, and 6MWD after treatment (375 mg/m^2 every wk for 1 mo)
Kavuru et al. [98]	2011	Phase II, single-site, open label	10	Rituximab	78% response; improved PaO2, A-aDO_2, spirometric data, and radiographic findings; reduced levels of BAL GM-CSF IgG autoantibodies, which correlated with disease severity; no change to autoantibodies in sera
Malur et al. [99]	2012	Phase II, single-site, open label	10	Rituximab	Follow-up analysis of BAL from above study showed rituximab increased expression of mRNA levels for PPARγ, ABCG1, and LPLA2 proteins; oil-red-o intensity of AM was reduced post-treatment
Soyez et al. [100]	2018	Retrospective, observational	13	Rituximab	30% response with improved A-aDO_2 after 12 mo but otherwise no clinical improvement; patients without prior specific therapy or higher levels of GM-CSF autoantibodies were more likely to demonstrate response

Table 2 (continued)

Study	Year	Trial Design	*N*	Drug	Findings
Bird et al. [97]	2022	Case study	1	Rituximab	Treatment (1000 mg IV on d 1 and 15) resulted in improved PaO2, A-aDO_2, spirometric data, radiographic findings, and 6MWD after 6 mo in patient with failed response to multiple prior WLL
Kavuru et al. [101]	2003	Case study	1	Plasmapheresis	Treatment (10 sessions of 1.5 L plasma volume exchanges over 2 mo) resulted in improved symptoms, PaO2, and radiographic findings in patient with failed response to WLL and subcutaneous GM-CSF
Luisetti et al. [102]	2009	Case study	1	Plasmapheresis	Treatment (10 sessions of 1.5 L plasma volume exchanges over 2 mo) lowered autoantibody titer but did not reflect clinical improvement in a patient with multiple prior WLL
Garber et al. [103]	2015	Case study	1	Plasmapheresis	Treatment (5 sessions of 1.5 L plasma volume exchanges over 5 consecutive d → rituximab) lowered autoantibody titer accompanied by improved symptoms and DLCO
Keske et al. [104]	2022	Case study	1	Plasmapheresis	Treatment (5 sessions in 6 d → 5 sessions in 9 d → rituximab) failed to produce clinical benefit in a patient with failed response to prior WLL and inhaled GM-CSF

Response rates and findings are reported as detailed; authors defer differentiation of intention-to-treat and per-protocol analysis to individual studies

Definition of abbreviations: *A-aDO_2* Alveolar-arterial oxygen gradient, *ABCG1* ATP binding cassette subfamily G member 1, *AM* alveolar macrophage, *BAL* bronchoalveolar lavage, *DLCO* diffusing capacity for carbon monoxide, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *HRCT* high-resolution computed tomography, *IgG* immunoglobulin G, *LPLA2* lysosomal phospholipase A2, *PaO2* partial pressure of oxygen in the arterial blood, *PAP* pulmonary alveolar proteinosis, *PPARγ* peroxisome proliferator-activated receptor gamma, *WLL* whole lung lavage, *6MWD* 6-min walk distance, *D* day, *MO* month, *WK* week

as LXR- α and ABCA1, pharmacologic correction of this pathway was investigated in murine models [85]. Molecular targeting of PPARγ with pioglitazone, an oral agonist, resulted in elevated mRNA transcript levels for ABCG1 and ABCA1 transporter proteins in alveolar macrophages as well as reduced cholesterol levels and lavage turbidity in PAP-afflicted mice. Administration of LXRα agonist T0901317, although not currently approved for human use, exhibited similar positive findings. A 2020 case study of a patient with autoimmune PAP with disease progression after multiple whole lung lavage treatments, inhaled GM-CSF, rituximab, and subcutaneous GM-CSF exhibited modest clinical improvement (i.e., symptoms, radiographic disease severity) following 12 months of oral pioglitazone therapy [86]. An assay measuring reactive oxygen species production of neutrophils and monocytes showed levels were comparable to a healthy control and significantly different from treatment-naïve patients with PAP. Another study of a patient with autoimmune PAP treated with pioglitazone showed a significant decrease in mean alveolar macrophage size as well as a nonsignificant trend towards reduced periodic acid-Schiff-positive stained material [87]. Recently, a 2024 study analyzed the lipidomic profile of 8 patients with autoimmune PAP compared to 11 healthy controls [88]. There was remarkable heterogeneity in the lipid profile of patients with PAP. Overall, the total alveolar macrophage lipid burden was increased in patients with PAP when compared to the control group. Furthermore, in patients with PAP, elevated lipid content was significantly associated with pulmonary fibrosis. Importantly, in a subset of patients with PAP who demonstrated clinical improvement following treatment with a range of therapies, including GM-CSF augmentation, statins, pioglitazone, rituximab, and plasmapheresis, repeat profiling of the alveolar macrophages showed reduced total lipid content and overall levels of major lipid classes.

The findings from these studies indicate lipid-targeted therapies may serve as an adjunct treatment in patients with PAP. Routine profiling of macrophage-associated lipids can assist in measuring treatment response. Future therapies may include aerosolized pioglitazone, LXRα agonism, and inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) [89, 90].

Immunomodulation

The production of GM-CSF autoantibodies in autoimmune PAP naturally motivates interest in immunomodulatory therapies (Table 2). Corticosteroid therapy has largely failed to produce clinical benefit in patients with PAP, with administration associated with worsening of disease severity as well as an elevated risk of opportunistic infection [91–93]. Stimulators of B-lymphocyte and immunoglobulin G production (i.e., B-cell activating factor, A proliferation-inducing ligand) are elevated in patients with autoimmune

PAP and negatively associated with various laboratory parameters, suggesting a role for B-lymphocyte depletion therapy [94]. Case studies of anti-CD20 rituximab in patients with autoimmune PAP indicated clinical benefit with or without prior whole lung lavage therapy [95–97]. A 2011 phase II, single-site, open label study administered intravenous rituximab to 10 patients with PAP [98]. PaO2, A-aDO_2, spirometric data, and radiographic findings improved in 7 of 9 patients who completed the study. Peripheral blood CD19 + B-lymphocytes were reduced for at least 3 months. Total levels of GM-CSF IgG autoantibodies were reduced in bronchoalveolar lavage fluid, correlating with disease severity, but not in sera after 6 months. Follow-up analysis also showed that rituximab increased mRNA expression for PPARγ and ABCG1 proteins as well as mRNA expression for lysosomal phospholipase A2, an enzyme involved in surfactant degradation [99]. However, a subsequent retrospective study of 13 patients treated with rituximab failed to show a significant or sustained clinical response to therapy [100]. Plasmapheresis has been employed in refractory cases of PAP to effectively remove the disease-causing autoantibody [101–104]. However, a sustained clinical response has only variably been achieved even with consistently reduced anti–GM-CSF antibody titers. Although not yet reported in cases of autoimmune PAP, intravenous immunoglobulin is a biological agent that may be of future interest for treatment.

Lung Transplantation

Lung transplantation for end-stage autoimmune PAP has only rarely been described [105, 106]. While there can be significant laboratory, radiographic, and clinical improvement after the procedure, the risk for recurrence remains and the patient should receive long-term follow-up at a specialized care center.

Conclusion

Autoimmune PAP is a disease of disordered surfactant clearance mediated by polyclonal anti-GM-CSF antibodies, the measurement of which remains the cornerstone of diagnosis. Understanding of its pathogenesis has advanced to emphasize dysregulated cholesterol efflux as a principal mechanistic driver of this disease. Whole lung lavage therapy remains the primary treatment modality, although prospective trials and standardization of the procedure are needed. Augmentation with recombinant human GM-CSF therapy likely improves clinical outcomes, particularly as a continuous inhaled administration. Lipid-targeting agents are emerging as noteworthy adjunct therapies. Investigations of emerging therapies are actively ongoing.

Abbreviations ABCA1: ATP binding cassette subfamily A member 1; ABCG1: ATP binding cassette subfamily G member 1; A-aDO_2: Alveolar-arterial oxygen gradient; DLCO: Diffusing capacity for carbon monoxide; GM-CSF: Granulocyte–macrophage colony-stimulating factor; PaO2: Partial pressure of oxygen in the arterial blood; PAP: Pulmonary alveolar proteinosis; PPAR-γ: Peroxisome proliferator-activated receptor gamma; PU.1: Purine-rich box1; 6MWD: 6-Minute walk distance

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Miyashita K, Hozumi H, Inoue Y, Suzuki T, Suda T. Nationwide survey of adult patients with pulmonary alveolar proteinosis using the National Database of designated intractable diseases of Japan. Respir Investig. 2023;61:364–70. https://doi.org/10.1016/j.resinv.2023.02.011.
2. McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. Orphanet J Rare Dis. 2018;13:129. https://doi.org/10.1186/s13023-018-0846-y.
3. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med. 1958;258:1123–42. https://doi.org/10.1056/NEJM195806052582301.
4. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003;349:2527–39. https://doi.org/10.1056/NEJMra023226.
5.• McCarthy C, Carey BC, Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2022;205:1016–35. https://doi.org/10.1164/rccm.

202112-2742SO. **State of the art comprehensive review of autoimmune pulmonary alveolar proteinosis**.
6. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med. 2008;177:752–62. https://doi.org/10.1164/rccm.200708-1271OC.
7. Han S, Mallampalli RK. The Role of Surfactant in Lung Disease and Host Defense against Pulmonary Infections. Ann Am Thorac Soc. 2015;12:765–74. https://doi.org/10.1513/AnnalsATS.201411-507FR.
8. Gschwend J, Sherman SPM, Ridder F, Feng X, Liang H-E, Locksley RM, et al. Alveolar macrophages rely on GM-CSF from alveolar epithelial type 2 cells before and after birth. J Exp Med. 2021. https://doi.org/10.1084/jem.20210745.
9. Schneider C, Nobs SP, Kurrer M, Rehrauer H, Thiele C, Kopf M. Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat Immunol. 2014;15:1026–37. https://doi.org/10.1038/ni.3005.
10. Wojcik AJ, Skaflen MD, Srinivasan S, Hedrick CC. A critical role for ABCG1 in macrophage inflammation and lung homeostasis. J Immunol. 2008;180:4273–82. https://doi.org/10.4049/jimmunol.180.6.4273.
11. Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol. 2018;14:452–63. https://doi.org/10.1038/s41574-018-0037-x.
12. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers. 2019;5:16. https://doi.org/10.1038/s41572-019-0066-3.
13. McCarthy C, Lee E, Bridges JP, Sallese A, Suzuki T, Woods JC, et al. Statin as a novel pharmacotherapy of pulmonary alveolar proteinosis. Nat Commun. 2018;9:3127. https://doi.org/10.1038/s41467-018-05491-z.
14. Sakagami T, Uchida K, Suzuki T, Carey BC, Wood RE, Wert SE, et al. Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis. N Engl J Med. 2009;361:2679–81. https://doi.org/10.1056/NEJMc0904077.
15. Dhagat U, Hercus TR, Broughton SE, Nero TL, Cheung Tung Shing KS, Barry EF, et al. The mechanism of GM-CSF inhibition by human GM-CSF auto-antibodies suggests novel therapeutic opportunities. MAbs. 2018;10:1018–29. https://doi.org/10.1080/19420862.2018.1494107.
16. Uchida K. High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. Blood. 2003;103:1089–98. https://doi.org/10.1182/blood-2003-05-1565.
17. Hwang JA, Song JH, Kim JH, Chung MP, Kim DS, Song JW, et al. Clinical significance of cigarette smoking and dust exposure in pulmonary alveolar proteinosis: a Korean national survey. BMC Pulm Med. 2017;17:147. https://doi.org/10.1186/s12890-017-0493-4.
18. Uchida K, Nakata K, Suzuki T, Luisetti M, Watanabe M, Koch DE, et al. Granulocyte/macrophage-colony-stimulating factor autoantibodies and myeloid cell immune functions in healthy subjects. Blood. 2009;113:2547–56. https://doi.org/10.1182/blood-2009-05-155689.
19. Seymour JF, Doyle IR, Nakata K, Presneill JJ, Schoch OD, Hamano E, et al. Relationship of anti-GM-CSF antibody concentration, surfactant protein A and B levels, and serum LDH to pulmonary parameters and response to GM-CSF therapy in patients with idiopathic alveolar proteinosis. Thorax. 2003;58:252–7. https://doi.org/10.1136/thorax.58.3.252.
20. Ataya A, Knight V, Carey BC, Lee E, Tarling EJ, Wang T. The Role of GM-CSF Autoantibodies in Infection and Autoimmune Pulmonary Alveolar Proteinosis: A Concise Review. Front Immunol. 2021;12: 752856. https://doi.org/10.3389/fimmu.2021.752856.
21. Mabo A, Borie R, Wemeau-Stervinou L, Uzunhan Y, Gomez E, Prevot G, et al. Infections in autoimmune pulmonary alveolar proteinosis: a large retrospective cohort. Thorax. 2023;79:68–74. https://doi.org/10.1136/thorax-2023-220040.
22. Trapnell BC, Carey BC, Uchida K, Suzuki T. Pulmonary alveolar proteinosis, a primary immunodeficiency of impaired GM-CSF stimulation of macrophages. Curr Opin Immunol. 2009;21:514–21. https://doi.org/10.1016/j.coi.2009.09.004.
23. Trapnell BC, Whitsett JA. GM-CSF Regulates Pulmonary Surfactant Homeostasis and Alveolar Macrophage-Mediated Innate Host Defense. Annu Rev Physiol. 2002;64:775–802. https://doi.org/10.1146/annurev.physiol.64.090601.113847.
24. Campo I, Mariani F, Rodi G, Paracchini E, Tsana E, Piloni D, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis. 2013;8:40. https://doi.org/10.1186/1750-1172-8-40.
25. Hawkins P, Chawke L, Cormican L, Wikenheiser-Brokamp KA, Fabre A, Keane MP, et al. Autoimmune pulmonary alveolar proteinosis: a discrepancy between symptoms and CT findings. Lancet. 2021;398: e7. https://doi.org/10.1016/S0140-6736(21)01254-X.
26. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med. 2002;166:215–35. https://doi.org/10.1164/rccm.2109105.
27. Punatar AD, Kusne S, Blair JE, Seville MT, Vikram HR. Opportunistic infections in patients with pulmonary alveolar proteinosis. J Infect. 2012;65:173–9. https://doi.org/10.1016/j.jinf.2012.03.020.
28. Mariani F, Infusino C, Lettieri S, Piloni D, Bosio M, De Silvestri A, et al. Lung fibrosis in Pulmonary Alveolar Proteinosis (PAP): different stages of a syndrome or distinct diseases? Rare ILD / DPLD. European Respiratory Society. 2021. https://doi.org/10.1183/13993003.congress-2021.PA2369.
29. Hunt AN, Malur A, Monfort T, Lagoudakis P, Mahajan S, Postle AD, et al. Hepatic Steatosis Accompanies Pulmonary Alveolar Proteinosis. Am J Respir Cell Mol Biol. 2017;57:448–58. https://doi.org/10.1165/rcmb.2016-0242OC.
30. Seymour JF. Extra-pulmonary aspects of acquired pulmonary alveolar proteinosis as predicted by granulocyte-macrophage colony-stimulating factor-deficient mice. Respirology. 2006. https://doi.org/10.1111/j.1440-1843.2006.00801.x.
31. Da Nam B, Kim TJ, Chung MP, Chung MJ, Kim TS, Lee KS. CT findings in pulmonary alveolar proteinosis: serial changes and prognostic implications. J Thorac Dis. 2018;10:5774–83. https://doi.org/10.21037/jtd.2018.09.86.
32. Fijołek J, Wiatr E, Radzikowska E, Bestry I, Langfort R, Polubiec-Kownacka M, et al. Pulmonary alveolar proteinosis during a 30-year observation. Diagnosis and treatment Pneumonol Alergol Pol. 2014;82:206–17. https://doi.org/10.5603/PiAP.2014.0028.
33. Uchida K, Nakata K, Carey B, Chalk C, Suzuki T, Sakagami T, et al. Standardized serum GM-CSF autoantibody testing for the routine clinical diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods. 2014;402:57–70. https://doi.org/10.1016/j.jim.2013.11.011.
34.•• McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. Chest. 2019;155:450–2. https://doi.org/10.1016/j.chest.2018.11.002. **Paper highlighting the importance of blood GM-CSF testing in diagnosing autoimmune pulmonary alveolar proteinosis**.
35. Nakata K, Sugi T, Kuroda K, Yoshizawa K, Takada T, Tazawa R, et al. Validation of a new serum granulocyte-macrophage

colony-stimulating factor autoantibody testing kit. ERJ Open Res. 2020. https://doi.org/10.1183/23120541.00259-2019.
36. Carey B, Chalk C, Stock J, Toth A, Klingler M, Greenberg H, et al. A dried blood spot test for diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods. 2022;511:113366. https://doi.org/10.1016/j.jim.2022.113366.
37. Suzuki T, Sakagami T, Rubin BK, Nogee LM, Wood RE, Zimmerman SL, et al. Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. J Exp Med. 2008;205:2703–10. https://doi.org/10.1084/jem.20080990.
38. Kusakabe Y, Uchida K, Hiruma T, Suzuki Y, Totsu T, Suzuki T, et al. A standardized blood test for the routine clinical diagnosis of impaired GM-CSF signaling using flow cytometry. J Immunol Methods. 2014;413:1–11. https://doi.org/10.1016/j.jim.2014.07.009.
39. Salvator H, Cheng A, Rosen LB, Williamson PR, Bennett JE, Kashyap A, et al. Neutralizing GM-CSF autoantibodies in pulmonary alveolar proteinosis, cryptococcal meningitis and severe nocardiosis. Respir Res. 2022;23:280. https://doi.org/10.1186/s12931-022-02103-9.
40. Lee E, Miller C, Ataya A, Wang T. Opportunistic Infection Associated With Elevated GM-CSF Autoantibodies: A Case Series and Review of the Literature. Open Forum Infect Dis. 2022;9:ofac146. https://doi.org/10.1093/ofid/ofac146.
41. Campo I, Meloni F, Gahlemann M, Sauter W, Ittrich C, Schoelch C, et al. An exploratory study investigating biomarkers associated with autoimmune pulmonary alveolar proteinosis (aPAP). Sci Rep. 2022;12:8708. https://doi.org/10.1038/s41598-022-11446-8.
42. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis. 2016;11:115. https://doi.org/10.1186/s13023-016-0497-9.
43. Wayne MT, Ali MS, Roller L, Gay SE, Maldonado F, De Cardenas J. Safety of Bilateral Whole Lung Lavage for Pulmonary Alveolar Proteinosis. J Bronchology Interv Pulmonol. 2023;30:188–91. https://doi.org/10.1097/LBR.0000000000000897.
44. Mariani F, Salvaterra E, Lettieri S, De Silvestri A, Corino A, Bosio M, et al. A mini-whole lung lavage to treat autoimmune pulmonary alveolar proteinosis (PAP). Respir Res. 2022;23:60. https://doi.org/10.1186/s12931-022-01982-2.
45. Ra SW, Park SE, Lee HK, Han IS, Park SH. Whole lung lavage using a rapid infusion system to treat a patient with pulmonary alveolar proteinosis. Yeungnam Univ J Med. 2020;37:67–72. https://doi.org/10.12701/yujm.2019.00360.
46. Gómez-Sánchez R, Santa-Teresa P, García López JJ, Duque P, García-Carreño J, Jaspe A. Pulmonary alveolar proteinosis treated with whole-lung lavage under veno-venous extracorporeal membrane oxygenation, clinical case series and review of the literature. Med Intensiva. 2024;48:59–61. https://doi.org/10.1016/j.medine.2023.11.005.
47. Bonella F, Bauer PC, Griese M, Wessendorf TE, Guzman J, Costabel U. Wash-out kinetics and efficacy of a modified lavage technique for alveolar proteinosis. Eur Respir J. 2012;40:1468–74. https://doi.org/10.1183/09031936.00017612.
48. Kinthala S, Liang M, Khusid F, Harrison S. The Use of High-Frequency Percussive Ventilation for Whole-Lung Lavage: A Case Report. A A Pract. 2018;11:205–7. https://doi.org/10.1213/XAA.0000000000000778.
49. McCarthy C, Bartholmai BJ, Woods JC, McCormack FX, Trapnell BC. Automated Parenchymal Pattern Analysis of Treatment Responses in Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2019;199:1151–2. https://doi.org/10.1164/rccm.201810-1918IM.
50. Zhang H-T, Wang C, Wang C-Y, Fang S-C, Xu B, Zhang Y-M. Efficacy of Whole-Lung Lavage in Treatment of Pulmonary Alveolar Proteinosis. Am J Ther. 2016;23:e1671–9. https://doi.org/10.1097/MJT.0000000000000239.
51. Kaenmuang P, Navasakulpong A. Efficacy of whole lung lavage in pulmonary alveolar proteinosis: a 20-year experience at a reference center in Thailand. J Thorac Dis. 2021;13:3539–48. https://doi.org/10.21037/jtd-20-3308.
52. Kiani A, Parsa T, Adimi Naghan P, Dutau H, Razavi F, Farzanegan B, et al. An eleven-year retrospective cross-sectional study on pulmonary alveolar proteinosis. Adv Respir Med. 2018;86:7–12. https://doi.org/10.5603/ARM.2018.0003.
53. Chuang C-H, Cheng C-H, Tsai Y-C, Tsai M-J, Sheu C-C, Chong I-W. Pulmonary alveolar proteinosis in Taiwan. J Formos Med Assoc. 2023;122:1061–8. https://doi.org/10.1016/j.jfma.2023.04.002.
54. Seymour JF, Dunn AR, Vincent JM, Presneill JJ, Pain MC. Efficacy of Granulocyte-Macrophage Colony-Stimulating Factor in Acquired Alveolar Proteinosis. N Engl J Med. 1996;335:1924–5. https://doi.org/10.1056/NEJM199612193352513.
55. Kavuru MS, Sullivan EJ, Piccin R, Thomassen MJ, Stoller JK. Exogenous Granulocyte-Macrophage Colony-Stimulating Factor Administration for Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2000;161:1143–8. https://doi.org/10.1164/ajrccm.161.4.9906044.
56. Seymour JF, Presneill JJ, Schoch OD, Downie GH, Moore PE, Doyle IR, et al. Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med. 2001;163:524–31. https://doi.org/10.1164/ajrccm.163.2.2003146.
57. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, et al. An Open-Label Trial of Granulocyte Macrophage Colony Stimulating Factor Therapy for Moderate Symptomatic Pulmonary Alveolar Proteinosis. Chest. 2006;130:227–37. https://doi.org/10.1378/chest.130.1.227.
58. Khan A, Agarwal R, Aggarwal AN, Bal A, Sen I, Yaddanapuddi LN, et al. Experience with treatment of pulmonary alveolar proteinosis from a tertiary care centre in north India. Indian J Chest Dis Allied Sci. 2012;54:91–7.
59. Hadda V, Tiwari P, Madan K, Mohan A, Gupta N, Bharti S, et al. Pulmonary alveolar proteinosis: Experience from a tertiary care center and systematic review of Indian literature. Lung India. 2016;33:626. https://doi.org/10.4103/0970-2113.192876.
60. Arai T, Hamano E, Inoue Y, Ryushi T, Nukiwa T, Sakatani M, et al. Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. Respir Med. 2004;98:1227–30. https://doi.org/10.1016/j.rmed.2004.08.011.
61. Tazawa R, Hamano E, Arai T, Ohta H, Ishimoto O, Uchida K, et al. Granulocyte-Macrophage Colony-Stimulating Factor and Lung Immunity in Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2005;171:1142–9. https://doi.org/10.1164/rccm.200406-716OC.
62. Wylam ME. Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis. Eur Respir J. 2006;27:585–93. https://doi.org/10.1183/09031936.06.00058305.
63. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, et al. Inhaled Granulocyte/Macrophage–Colony Stimulating Factor as Therapy for Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2010;181:1345–54. https://doi.org/10.1164/rccm.200906-0978OC.
64. Ohashi K, Sato A, Takada T, Arai T, Nei T, Kasahara Y, et al. Direct evidence that GM-CSF inhalation improves lung clearance in pulmonary alveolar proteinosis. Respir Med. 2012;106:284–93. https://doi.org/10.1016/j.rmed.2011.10.019.
65. Papiris SA, Tsirigotis P, Kolilekas L, Papadaki G, Papaioannou AI, Triantafillidou C, et al. Long-Term Inhaled Granulocyte Macrophage–Colony-Stimulating Factor in Autoimmune

Pulmonary Alveolar Proteinosis: Effectiveness, Safety, and Lowest Effective Dose. Clin Drug Investig. 2014;34:553–64. https://doi.org/10.1007/s40261-014-0208-z.

66. Campo I, Mariani F, Paracchini E, Kadija Z, Zorzetto M, Tinelli C, et al. Inhaled sargramostim and whole lung lavage (WLL) as therapy of autoimmune pulmonary alveolar proteinosis (aPAP). Diffuse Parenchymal Lung Disease European Respiratory Society. 2016. https://doi.org/10.1183/13993003.congress-2016.PA3870.
67. Ohkouchi S, Akasaka K, Ichiwata T, Hisata S, Iijima H, Takada T, et al. Sequential Granulocyte-Macrophage Colony-Stimulating Factor Inhalation after Whole-Lung Lavage for Pulmonary Alveolar Proteinosis A Report of Five Intractable Cases. Ann Am Thorac Soc. 2017;14:1298–304. https://doi.org/10.1513/AnnalsATS.201611-892BC.
68. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, et al. Inhaled GM-CSF for Pulmonary Alveolar Proteinosis. N Engl J Med. 2019;381:923–32. https://doi.org/10.1056/NEJMoa1816216.
69. Zhen G, Li D, Jiang J, Weng Y. Granulocyte-Macrophage Colony-Stimulating Factor Inhalation Therapy for Severe Pulmonary Alveolar Proteinosis. Am J Ther. 2020;28:e171–8. https://doi.org/10.1097/MJT.0000000000001053.
70. Tian X, Yang Y, Chen L, Sui X, Xu W, Li X, et al. Inhaled granulocyte-macrophage colony stimulating factor for mild-to-moderate autoimmune pulmonary alveolar proteinosis - a six month phase II randomized study with 24 months of follow-up. Orphanet J Rare Dis. 2020;15:174. https://doi.org/10.1186/s13023-020-01450-4.
71.•• Trapnell BC, Inoue Y, Bonella F, Morgan C, Jouneau S, Bendstrup E, et al. Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis. N Engl J Med. 2020;383:1635–44. https://doi.org/10.1056/NEJMoa1913590. **The largest randomized clinical trial in autoimmune PAP to date showing inhaled GM-CSF therapy was superior to placebo in improving multiple endpoints including change in arterial-alveolar gradient and diffusion capacity to carbon monoxide (DLCO)**.
72. Livingstone C, Corallo C, Siemienowicz M, Pilcher D, Stirling RG. Nebulised sargramostim in pulmonary alveolar proteinosis. Br J Clin Pharmacol. 2022;88:3523–8. https://doi.org/10.1111/bcp.15266.
73. Tazawa R, Inoue Y, Arai T, Takada T, Kasahara Y, Hojo M, et al. Duration of Benefit in Patients With Autoimmune Pulmonary Alveolar Proteinosis After Inhaled Granulocyte-Macrophage Colony-Stimulating Factor Therapy. Chest. 2014;145:729–37. https://doi.org/10.1378/chest.13-0603.
74. Sheng G, Chen P, Wei Y, Chu J, Cao X, Zhang H-L. Better approach for autoimmune pulmonary alveolar proteinosis treatment: inhaled or subcutaneous granulocyte-macrophage colony-stimulating factor: a meta-analyses. Respir Res. 2018;19:163. https://doi.org/10.1186/s12931-018-0862-4.
75. Zhang F, Weng D, Su Y, Yin C, Shen L, Zhang Y, et al. Therapeutic effect of subcutaneous injection of low dose recombinant human granulocyte-macrophage colony-stimulating factor on pulmonary alveolar proteinosis. Respir Res. 2020;21:1. https://doi.org/10.1186/s12931-019-1261-1.
76. Munsif M, Sweeney D, Leong TL, Stirling RG. Nebulised granulocyte–macrophage colony-stimulating factor (GM-CSF) in autoimmune pulmonary alveolar proteinosis: a systematic review and meta-analysis. Eur Respir Rev. 2023;32: 230080. https://doi.org/10.1183/16000617.0080-2023.
77. Campo I, Carey BC, Paracchini E, Kadija Z, De Silvestri A, Rodi G, et al. Inhaled recombinant GM-CSF reduces the need for whole lung lavage and improves gas exchange in autoimmune pulmonary alveolar proteinosis patients. Eur Respir J. 2024. https://doi.org/10.1183/13993003.01233-2023.
78. Trapnell BC, McCarthy C. The Alveolar Lipidome in Pulmonary Alveolar Proteinosis. A New Target for Therapeutic Development? Am J Respir Crit Care Med. 2019;200:800–2. https://doi.org/10.1164/rccm.201905-1009ED.
79. Yan X, Gao Y, Zhao Q, Qiu X, Tian M, Dai J, et al. Correlation of Lipid Ratios With the Severity of Pulmonary Alveolar Proteinosis: A Cross-Sectional Study. Front Nutr. 2021. https://doi.org/10.3389/fnut.2021.610765.
80. Griese M, Bonella F, Costabel U, de Blic J, Tran N-B, Liebisch G. Quantitative Lipidomics in Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med. 2019;200:881–7. https://doi.org/10.1164/rccm.201901-0086OC.
81. Shi S, Wang R, Chen L, Li Y, Zhang Y, Xin X, et al. Long-term follow-up and successful treatment of pulmonary alveolar proteinosis without hypercholesterolemia with statin therapy: a case report. J Int Med Res. 2021;49:3000605211010046. https://doi.org/10.1177/03000605211010046.
82. Takano T, Takeda K, Nakamura S, Akiyama G, Ando N, Komori M. A case of autoimmune pulmonary alveolar proteinosis with severe respiratory failure treated with segmental lung lavage and oral statin therapy. Respir Med Case Rep. 2022;38: 101684. https://doi.org/10.1016/j.rmcr.2022.101684.
83. Shi S, Gui X, Ding J, Yang S, Xin X, Xu K, et al. Assessment of Statin Treatment for Pulmonary Alveolar Proteinosis without Hypercholesterolemia: A 12-Month Prospective, Longitudinal, and Observational Study. Biomed Res Int. 2022;2022:1589660. https://doi.org/10.1155/2022/1589660.
84. Shi S, Zou R, Chen L, Yang S, Xu K, Xin X, et al. Quantitative chest CT assessment of pulmonary alveolar proteinosis with deep learning: a real-world longitudinal study. Quant Imaging Med Surg. 2022;12:5394–403. https://doi.org/10.21037/qims-22-205.
85. Sallese A, Suzuki T, McCarthy C, Bridges J, Filuta A, Arumugam P, et al. Targeting cholesterol homeostasis in lung diseases. Sci Rep. 2017;7:10211. https://doi.org/10.1038/s41598-017-10879-w.
86. Dupin C, Hurtado M, Cazes A, Taille C, Debray MP, Guenée C, et al. Pioglitazone in pulmonary alveolar proteinosis: promising first clinical experience. Respir Med Res. 2020;78: 100756. https://doi.org/10.1016/j.resmer.2020.100756.
87. Vis DC, Kelly MM, De Heuvel E, MacEachern PR. Reduction in Alveolar Macrophage Size in Refractory Autoimmune Pulmonary Alveolar Proteinosis After Treatment With Pioglitazone. J Bronchology Interv Pulmonol. 2020;27:219–22. https://doi.org/10.1097/LBR.0000000000000686.
88. Lee E, Williams KJ, McCarthy C, Bridges JP, Redente EF, de Aguiar Vallim TQ, et al. Alveolar macrophage lipid burden correlates with clinical improvement in patients with pulmonary alveolar proteinosis. J Lipid Res. 2024;65: 100496. https://doi.org/10.1016/j.jlr.2024.100496.
89. Seabloom DE, Galbraith AR, Haynes AM, Antonides JD, Wuertz BR, Miller WA, et al. Safety and Preclinical Efficacy of Aerosol Pioglitazone on Lung Adenoma Prevention in A/J Mice. Cancer Prev Res (Phila). 2017;10:124–32. https://doi.org/10.1158/1940-6207.CAPR-16-0174.
90. Huang J, Lin Z, Lin J, Xie S, Xia S, Chen G, et al. Causal role of lipid metabolism in pulmonary alveolar proteinosis: an observational and mendelian randomisation study. Thorax. 2024;79:135–43. https://doi.org/10.1136/thorax-2023-220789.
91. Akasaka K, Tanaka T, Kitamura N, Ohkouchi S, Tazawa R, Takada T, et al. Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis: a retrospective cohort study. BMC Pulm Med. 2015;15:88. https://doi.org/10.1186/s12890-015-0085-0.
92. Ishimoto H, Sakamoto N, Yura H, Hara A, Kido T, Yamaguchi H, et al. Autoimmune pulmonary alveolar proteinosis exacerbated by steroid therapy due to misdiagnosis as anti-aminoacyl-tRNA

synthetase (ARS) antibody positive- interstitial pneumonia: a case report. BMC Pulm Med. 2022;22:120. https://doi.org/10.1186/s12890-022-01909-z.
93. Asami-Noyama M, Ito K, Harada M, Hisamoto Y, Kunihiro Y, Ikeda E, et al. A case of development of autoimmune pulmonary alveolar proteinosis during the treatment of hypersensitivity pneumonitis. Respir Med Case Rep. 2023;44: 101862. https://doi.org/10.1016/j.rmcr.2023.101862.
94. Hirose M, Arai T, Sugimoto C, Takimoto T, Sugawara R, Minomo S, et al. B cell-activating factors in autoimmune pulmonary alveolar proteinosis. Orphanet J Rare Dis. 2021;16:115. https://doi.org/10.1186/s13023-021-01755-y.
95. Borie R, Debray M-P, Laine C, Aubier M, Crestani B. Rituximab therapy in autoimmune pulmonary alveolar proteinosis. Eur Respir J. 2009;33:1503–6. https://doi.org/10.1183/09031936.00160908.
96. Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. Thorax. 2010;65:1025–6. https://doi.org/10.1136/thx.2010.140673.
97. Bird D, Evans J, Pahoff C. Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis. Respir Med Case Rep. 2022;37: 101637. https://doi.org/10.1016/j.rmcr.2022.101637.
98. Kavuru MS, Malur A, Marshall I, Barna BP, Meziane M, Huizar I, et al. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J. 2011;38:1361–7. https://doi.org/10.1183/09031936.00197710.
99. Malur A, Kavuru MS, Marshall I, Barna BP, Huizar I, Karnekar R, et al. Rituximab therapy in pulmonary alveolar proteinosis improves alveolar macrophage lipid homeostasis. Respir Res. 2012;13:46. https://doi.org/10.1186/1465-9921-13-46.
100. Soyez B, Borie R, Menard C, Cadranel J, Chavez L, Cottin V, et al. Rituximab for auto-immune alveolar proteinosis, a real life cohort study. Respir Res. 2018;19:74. https://doi.org/10.1186/s12931-018-0780-5.
101. Kavuru MS, Bonfield TL, Thomassen MJ. Plasmapheresis, GM-CSF, and alveolar proteinosis. Am J Respir Crit Care Med. 2003;167:1036–7. https://doi.org/10.1164/ajrccm.167.7.950.
102. Luisetti M, Rodi G, Perotti C, Campo I, Mariani F, Pozzi E, et al. Plasmapheresis for treatment of pulmonary alveolar proteinosis. Eur Respir J. 2009;33:1220–2. https://doi.org/10.1183/09031936.00097508.
103. Garber B, Albores J, Wang T, Neville TH. A Plasmapheresis Protocol for Refractory Pulmonary Alveolar Proteinosis. Lung. 2015;193:209–11. https://doi.org/10.1007/s00408-014-9678-2.
104. Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary Alveolar Proteinosis Refractory to Plasmapheresis and Rituximab despite GM-CSF Antibody Reduction. Case Reports Immunol. 2022;2022:2104270. https://doi.org/10.1155/2022/2104270.
105. Parker LA, Novotny DB. Recurrent alveolar proteinosis following double lung transplantation. Chest. 1997;111:1457–8. https://doi.org/10.1378/chest.111.5.1457.
106. Wang YB, Li FK, Ding ZD, Zhao K, Fang ZM, Feng M, et al. Lung transplantation for pulmonary alveolar proteinosis: a case report and literature review. Zhonghua Jie He He Hu Xi Za Zhi. 2022;45:667–70. https://doi.org/10.3760/cma.j.cn112147-20220302-00165.