Long-term outcomes in five patients with autoimmune pulmonary alveolar proteinosis treated with molgramostim inhalation solution

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To the Editor:

Autoimmune pulmonary alveolar proteinosis (aPAP), which accounts for >90% of all cases of PAP, is a rare lung disease mediated by granulocyte–macrophage colony-stimulating factor (GM-CSF) autoantibodies that block GM-CSF signalling, leading to reduced surfactant clearance causing abnormal accumulation of alveolar surfactant and impaired gas exchange [1–3]. The current standard of care for aPAP is whole-lung lavage (WLL), which is invasive, resource intensive, carries procedural risk, does not address the underlying cause of disease and often must be repeated regularly [4]. Hence, there is a therapeutical need to address the underlying pathophysiology of the disease. Studies have explored inhaled GM-CSF augmentation as a primary treatment for aPAP [5–12]. In this real-world case series, we present the beneficial long-term effects of molgramostim inhalation solution, an investigational, recombinant GM-CSF, in five aPAP patients with therapeutic disease challenges.

All five patients had classic computed tomography (CT) scan patterns, bronchoalveolar lavage findings and characteristic PAP symptoms coupled with a positive GM-CSF autoantibody test, leading to a diagnosis of aPAP. All patients received inhaled molgramostim administered using a vibrating mesh nebuliser (eFlow, PARI Pharma) as part of a compassionate-use programme established by Savara Inc. and in compliance with regulations in the patients' countries. Table 1 shows high-resolution CT scans and clinical measures for each patient before treatment with molgramostim and after remaining on therapy for varying periods. There were no reported serious adverse events in these five patients while receiving molgramostim and the treatment has been well tolerated.

Patient 1 was a male diagnosed with aPAP at 27 years of age and presented with a 2-month history of progressive dyspnoea requiring 8 $L \cdot min^{-1}$ oxygen at rest. In February 2019, a WLL was performed once on the left side and 3 months later, on the right side. Given that this was a young patient with severely impaired lung function, severe limitation of daily activities and the need for supplemental oxygen, the patient began therapy with molgramostim in June 2019. After starting therapy, steady clinical improvement was observed with a 54% increase in predicted diffusing capacity of the lung for carbon monoxide (D_{LCO}), and a simultaneous decrease in the need for supplemental oxygen and increases in tolerance to physical exertion. Currently, the patient is leading a self-described "normal everyday life" and can work as he did before the onset of the disease.

Patient 2 was a female who presented in December 2018 at age 28 with 3 days of influenza-like symptoms including musculoskeletal pain, fever, vomiting, diarrhoea and progressive breathlessness. She was hospitalised and immediately transferred to the intensive care unit due to respiratory failure. In March 2020, the patient presented to a specialised interstitial lung disease clinic with cough and progressive dyspnoea. Molgramostim was started immediately after diagnosis of aPAP in March 2020, and the patient showed significant improvement in D_{LCO} and forced vital capacity.

In patient 3, diagnosis of aPAP was made at 31 years of age. He worked as a technical engineer and was subjected to dust exposure. The patient had been stable for 4 years without any treatment. However, in July

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This real-world case series presents the beneficial long-term effects of molgramostim inhalation solution, an investigational, recombinant GM-CSF, in five patients with severe aPAP who received molgramostim on a compassionate-use basis https://bit.ly/3ypPhJl

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TABLE 1 Presentation and treatment of five adults with autoimmune pulmonary alveolar proteinosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at presentation (years)	27	29	31	21	46
Age at last follow-up (years)	31	33	40	32	52
Sex	Male	Female	Male	Female	Male
Initial presentation	Progressive dyspnoea, need 8 L·min^{-1} O_2 at rest	Influenza-like symptoms including muscle–joint pain, fever, vomiting, diarrhoea, and progressive breathlessness	Dyspnoea, cough, need 4 L·min^{-1} O_2 at rest	Cough and progressive exertional dyspnoea and chest tightness	Cough, chest pain, dyspnoea on exercise
CT scan with crazy-paving pattern	Yes	Yes	Yes	Yes	Yes
BAL with milky appearance, granular eosinophilic material	Yes	Yes	Not done	Yes	Yes
Lung biopsy with alveolar spaces filled with homogeneously eosinophilic, PAS-positive material	Yes	Not done	Yes	Yes	Not done
Anti-GM-CSF antibody	Positive	Positive	Positive	Positive	Positive
WLL number before/after	2 (within 1 year)/0	Not done	4 (within 1 year)/0	8 (within 4 years)/0	3 (within 1 year)/0
FVC (% pred) initial/last	64/74 10% increase	83/122 39% increase	52/71 19% increase	73/88 15% increase	54/75 21% increase
D_{Lco} (% pred) initial/last	37/91 54% increase	36/60 24% increase	39/87 48% increase	62/90 28% increase	12/44 32% increase
P_{aO_2} (mmHg) or S_{pO_2} (%) initial/last	56 mmHg/74 mmHg	90%/99%	95%/NA[#]	66.7 mmHg/85.4 mmHg	77 mmHg (with 3 L·min^{-1} O_2)/ 80 mmHg (room air)
Reduction in D_{A-aO_2} from initial visit to last follow-up (mmHg)	−47.4	NA	NA	−20.6	−52.9
Disease severity score Initial/last	4/1	4/2	4/NA[#]	3/1	5/2
Time on molgramostim (years)	4.5	3.5	5.5	4 and previous 1 year in IMPALA trial	1.5 and previous 1 year in IMPALA trial
Molgramostim dose	300 µg·day^{-1}	March 2020–Feb 2021, 250 µg·day^{-1} Feb 2021, 250 µg every other day March–April 2021, no treatment April 2021–May 2022, 250 µg·day^{-1} May 2022, 250 µg every other day until present	300 µg·day^{-1}	300 µg·day^{-1} every other week	Dec 2017–Dec 2018, 300 µg·day^{-1} every other week Dec 2018–Jan 2023, no treatment Jan 2023–present 300 µg·day^{-1}

Continued

TABLE 1 Continued

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical outcome	Overall improvement Decrease in oxygen demand Improved PFTs and radiological findings	Rapid clinical improvement Improved PFTs and radiological findings	Improved No longer needed O_2 supplementation Improved PFTs and radiological findings	Improved, without further need for O_2 supplementation Improved PFTs and radiological findings	Improved, without need for O_2 at rest Improved PFTs and radiological findings
HRCT before treatment with molgramostim inhalation solution	Jan 2019	March 2020	Jan 2018	Aug 2018	Dec 2022[¶]
HRCT after treatment with molgramostim inhalation solution	June 2020, after 1 year on molgramostim	Jan 2021, after 10 months on molgramostim	June 2023, after 3.5 years on molgramostim	Aug 2022, after 4 years on molgramostim	Feb 2024, after 14 months on molgramostim

CT: computed tomography; BAL: bronchoalveolar lavage; PAS: periodic acid–Schiff staining; GM-CSF: granulocyte–macrophage colony-stimulating factor; WLL: whole-lung lavage; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; S_{pO_2}: oxygen saturation measured by pulse oximetry; D_{A-aO_2}: alveolar–arterial oxygen concentration difference; NA: not available; PFT: pulmonary function test; HRCT: high-resolution computed tomography. [#]: there was no S_{pO_2} or disease severity score captured on last follow-up for patient 3; [¶]: HRCT after three WLLs that year and just after the third.

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2017, the patient presented with cough and required 4 $L \cdot min^{-1}$ oxygen at rest. In 2018, the patient underwent four WLLs within a period of 4 months (two times on the right and two times on the left). The patient began molgramostim in December 2018. The patient showed considerable improvement within the first year of therapy with reduced shortness of breath and cough, and he no longer required oxygen supplementation at rest. No further WLL was required after the initiation of molgramostim therapy.

Patient 4 was a 21-year-old female who presented in 2012 with a 6-month history of cough, progressive exertional dyspnoea and chest tightness. Because of worsening hypoxaemia, the patient underwent WLL, ultimately having eight WLLs over the course of 4 years. From September 2018 to September 2019, the patient was involved in a randomised controlled clinical trial evaluating the safety and efficacy of inhaled molgramostim in patients with aPAP (IMPALA trial) [12], and since January 2020, the patient has been on molgramostim without further need for WLL or oxygen supplementation. The patient reports that the most significant effects of being on molgramostim are reduction in tiredness and no longer requiring supplemental oxygen.

Patient 5, an athletic 46-year-old male, presented in 2017 with a 6-month history of cough, chest pain and shortness of breath on exertion; he could no longer run. From December 2017 to December 2018, he participated in the IMPALA trial [12], and after receiving molgramostim showed clinical, functional and radiological improvement. The patient was asymptomatic until 2021, when he reported progressive respiratory decline. He was admitted to the hospital three times for respiratory failure secondary to infections and disease progression. WLL was performed in both lungs three times in 2022 with partial improvement. The patient required oxygen supplementation at rest and was referred for an evaluation for lung transplantation. The patient restarted molgramostim in January 2023 with rapid and significant clinical, functional and radiological improvement. No WLL has been performed since then nor have there been further hospitalisations. Currently, the patient does not need supplemental oxygen and he has returned to work.

Patients with aPAP are frequently misdiagnosed with pneumonia based on radiological findings or asthma based on nonspecific symptoms until the failure to respond to “appropriate” therapy prompts reconsideration of the diagnosis; in such cases, an accurate diagnosis is delayed on average by 18 months [13]. Results from the US National PAP Registry indicate many patients with PAP undergo transbronchial biopsy, surgical lung biopsy or both even though neither is diagnostic for any PAP-causing disease, and both are associated with sampling error and significant procedure-related morbidity [13]. Despite our understanding of aPAP pathophysiology, the path to a definitive diagnosis can be challenging. However, the availability of a serum GM-CSF autoantibody test to diagnose aPAP has rendered lung biopsies unnecessary in most cases [14].

There are no data yet to support the long-term benefits of inhaled GM-CSF. In this case series, none of the five patients required WLL after >1 year on molgramostim, suggesting that molgramostim therapy may have prevented the need for WLL in these patients. Moreover, in one case, a patient received molgramostim as first-line therapy because of an inability to schedule a WLL and she ultimately avoided WLL completely. Furthermore, the improvements in disease severity, gas transfer measured by D_{LCO} and alveolar–arterial oxygen gradient when available, and activities of daily living were maintained over time. The main limitation of this case series is the retrospective nature of the data collected from real-world clinical practice.

An overarching theme in these patients’ stories is an apparent significant healthcare burden on aPAP patients in terms of initial misdiagnosis, procedures, therapy use, healthcare utilisation and costs. Patients with aPAP have significantly higher rates of healthcare utilisation and comorbidities, with 66% more outpatient visits, 38% more emergency department visits and hospital stays that are three times longer when compared with age- and gender-matched control patients [15].

The present data suggest that the use of molgramostim in a real-world clinical setting provides a pharmacological approach to addressing the underlying pathophysiology of aPAP resulting in improved lung function, decreased disease burden, restored patient functionality and reduction of clinical symptoms allowing for a resumption of activities of daily life.

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