

Regression of a Refractory Pulmonary Lesion in Granulomatosis with Polyangiitis Following the Addition of Avacopan

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Abstract

Avacopan, a complement component 5a (C5a) receptor antagonist, is an emerging therapeutic agent for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. However, its intrinsic efficacy remains unclear. A 74-year-old woman with granulomatosis with polyangiitis (GPA) presenting as a pulmonary mass, sinusitis, otitis media with hearing loss, and mononeuritis multiplex is reported. Initial remission was achieved with prednisolone and cyclophosphamide followed by maintenance with low-dose prednisolone and azathioprine. After 3 years, she relapsed with recurrent blood-stained sputum and enlargement of the pulmonary lesion despite negative ANCA titers. Infection and malignancy were excluded. Avacopan (60 mg/day) was introduced with low-dose prednisolone and azathioprine. Over 12 months, the pulmonary mass regressed, and blood-stained sputum improved, enabling complete withdrawal of prednisolone after 20 months. This case suggests a potential direct effect of avacopan on pulmonary inflammatory lesions in GPA and highlights the importance of long-term treatment evaluation.

Keywords: ANCA-associated vasculitis, avacopan, granulomatosis with polyangiitis, vasculitis

Introduction

Avacopan, a complement C5a receptor antagonist, has emerged as a promising therapeutic option for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) that mitigates neutrophil activation via complement inhibition.¹ This agent is expected to reduce or eliminate the need for glucocorticoids, which are central, but problematic in the management of vasculitis. In clinical settings, however, avacopan is frequently administered alongside cyclophosphamide or rituximab following the remission induction strategy outlined in the ADVOCATE (Avacopan Development in Vasculitis to Obtain Corticosteroid Elimination and Therapeutic Efficacy) trial.^{2,3}

To date, the intrinsic therapeutic effectiveness of avacopan remains unclear owing to the lack of established supporting evidence. Here, a case of granulomatosis with polyangiitis (GPA), wherein a refractory pulmonary mass lesion markedly regressed following the addition of avacopan is presented, suggesting a direct therapeutic effect of this drug.

Case Presentation

A 74-year-old woman was diagnosed with GPA. The patient initially presented with a pulmonary mass in the right upper lobe, mild blood-stained sputum, mild sensory impairment of the foot due to mononeuritis multiplex, sinusitis, hearing loss due to otitis media and mastoiditis. Laboratory findings revealed a white blood cell count of 6500/ μ L and eosinophil count of 300/ μ L. An elevated C-reactive protein (CRP) level of 2.23 mg/dL and myeloperoxidase (MPO)-ANCA titer of 51 IU/mL; proteinase 3-ANCA tested negative. According to the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for GPA, this patient was classified as GPA with a total score of 6 points: nasal involvement scored 3 points, hearing loss due to otitis media scored 1 point, chest imaging scored 2 points, paranasal sinus inflammation and mastoiditis on imaging scored 1 point, and pANCA (perinuclear) or MPO-ANCA positivity scored –1 point. Remission was induced with prednisolone (50 mg/day) and intravenous cyclophosphamide, followed by maintenance therapy with prednisolone (5 mg/day) and azathioprine (75 mg/day) for 3 years. During this period, both the CRP and ANCA levels remained negative. The pulmonary lesion showed partial regression but did not completely disappear after the initial induction therapy.

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However, the patient relapsed and exhibited a mildly elevated CRP level (0.51 mg/dL) and recurrent mild blood-stained sputum, along with an increase in the size of the pulmonary mass in the right upper lobe (Figure 1A). The MPO-ANCA test result was negative. Bronchoscopic evaluation, including bronchoalveolar lavage, ruled out tuberculosis and malignancy as potential causes of the pulmonary lesions; however, no biopsy was performed, and histological confirmation of granulomatous inflammation was not obtained. Avacopan was initiated at 60 mg/day, in addition to prednisolone (5 mg/day) and azathioprine (75 mg/day), with only a new pulmonary lesion detected on chest radiography (3 points in The Birmingham Vasculitis Activity Score (BVAS) version 3), and the case was therefore considered mild. Although treatment continued for 6 months, the mild blood-stained sputum persisted. Twelve months after the initiation of avacopan, chest computed tomography revealed a reduction in the mass in the right upper lobe (Figure 1B), accompanied by an improvement in mild blood-stained sputum. Therefore, the prednisolone was tapered from 5 mg/day by 1 mg every 2 months, eventually reaching 0 mg/day after 20 months of avacopan therapy, during which the pulmonary mass showed further regression on imaging (Figure 1C), while azathioprine was maintained at 75 mg/day throughout the course. A summary of the treatment course and clinical response is shown in Figure 2.

Discussion

The ADVOCATE trial, a phase 3 study of avacopan, compared patients who received standard immunosuppressive therapy plus glucocorticoids with those who received immunosuppressants plus avacopan. The avacopan group demonstrated superior rates of sustained remission at 52 weeks.^{2,3} However, it is important to note that patients in the avacopan group received an adequate glucocorticoid

course before randomization, and both groups were concomitantly treated with immunosuppressive agents. Therefore, the trial did not establish the efficacy of avacopan itself. Five cases of minor AAV relapses were reported previously, in which the addition of avacopan, without increasing the glucocorticoid dosage or introducing new immunosuppressive agents, failed to achieve clinical improvement.⁴ The present case is that of 1 of 5 patients who

initially showed no short-term response to avacopan but continued treatment beyond that period, ultimately demonstrating a delayed therapeutic benefit.

C5a is a potent chemoattractant and neutrophil activator. Avacopan selectively binds to the C5a receptor, thereby blocking the effects of C5a. This inhibition suppresses neutrophil priming and subsequent neutrophil activation

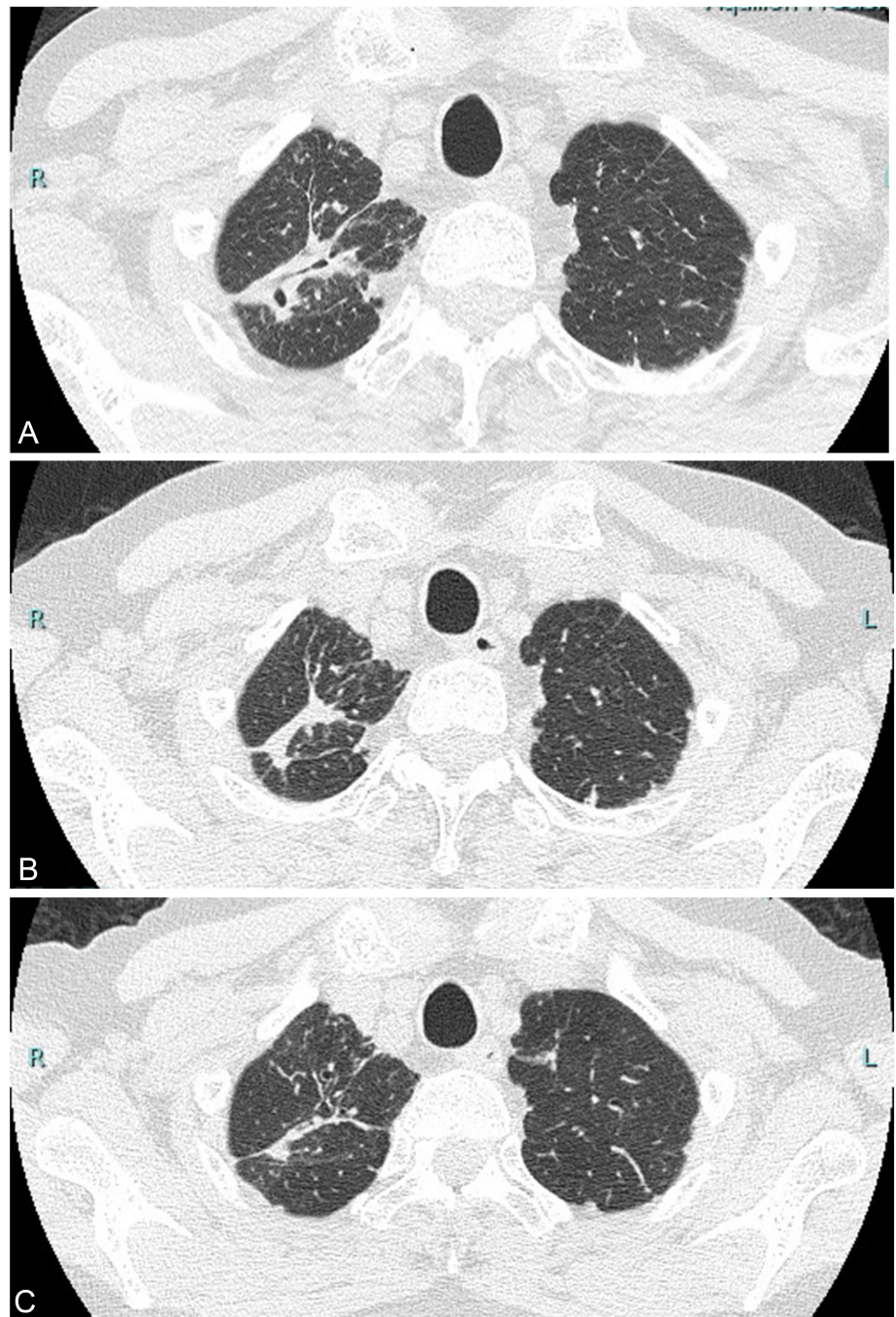


Figure 1. A: Pulmonary mass in the right upper lobe on computed tomography (CT) before avacopan administration. B: Pulmonary mass in the right upper lobe on CT 12 months after avacopan administration. C: Further regression of the pulmonary mass in the right upper lobe on CT 20 months after avacopan administration.

Main Points

- Avacopan may reduce pulmonary inflammatory lesions in granulomatosis with polyangiitis (GPA) without additional immunosuppressive therapy.
- Sustained avacopan treatment can induce delayed therapeutic benefits in refractory pulmonary GPA.
- Complement C5a inhibition may suppress granuloma formation by modulating neutrophil and macrophage recruitment.

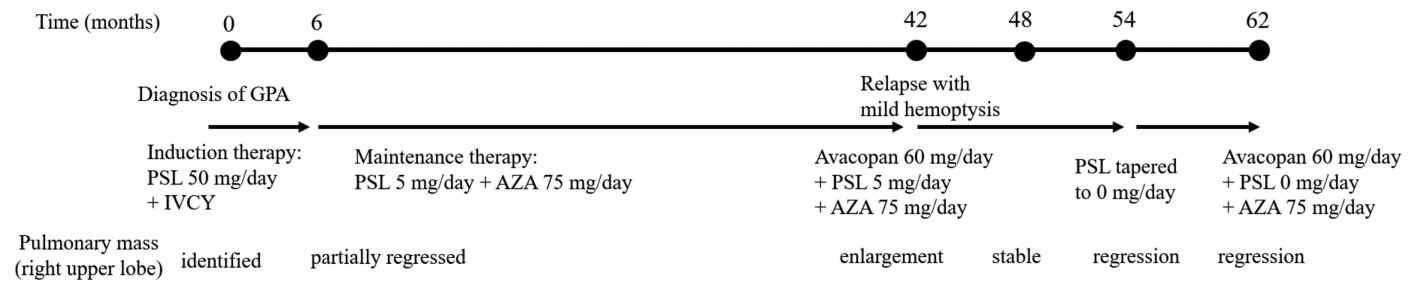


Figure 2. Clinical timeline of the patient with granulomatosis with polyangiitis treated with avacopan. AZA, azathioprine; GPA, granulomatosis with polyangiitis; IVCY, intravenous cyclophosphamide; PSL, prednisolone.

triggered by ANCA binding and vascular endothelial damage mediated by neutrophil extracellular traps and further amplifies the complement cascade.^{5,6}

Activation of the complement system may also play a role in granuloma formation. In particular, C5a acts as a potent pro-inflammatory mediator that promotes the recruitment of neutrophils and macrophages. Cellular accumulation at sites of inflammation may contribute to the development of granulomas. Studies in C5-deficient mice have demonstrated impaired granuloma formation in the absence of complement components, suggesting a critical role for complement in this process. Therefore, avacopan-mediated inhibition of C5a may suppress granulomatous inflammation in patients with GPA.^{7,8}

Although histological confirmation of granulomatous inflammation was not obtained in this case, it may be hypothesized that avacopan has a suppressive effect on inflammatory pulmonary lesions observed in GPA. It also highlights the importance of long-term observation to fully assess the therapeutic impact of avacopan.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was not required for the study.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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