

Imaging for precision medicine: can V-P SPECT measure mepolizumab response in asthma?

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Abstract

Monoclonal antibody therapies are effective for many but not all people with severe asthma. Precision medicine guides treatment selection using biomarkers to select patients most likely to respond according to their inflammatory endotypes. However, when assessing response to treatment, greater precision is required. We report a case series describing treatment response to mepolizumab in four severe asthma patients, assessed by traditional methods and with objective ventilation/perfusion single photon emission computed tomography (V-P SPECT). In this series, patients with severe asthma received mepolizumab treatment with clinical outcomes recorded at commencement and at approximately 16 weeks post-treatment initiation. V-P SPECT imaging was performed before and after treatment to determine ventilation heterogeneity and perfusion, and its ability to assess treatment responsiveness. V-P SPECT shows promise as an objective measure to assess lung ventilation and perfusion to observe and assess responsiveness to mepolizumab. With quantification, this measure may allow better precision in determining treatment improvements.

Introduction

Severe asthma management has significantly advanced in recent years with the introduction of targeted monoclonal antibody (mAb) therapies [1]. Type 2 (T₂)-targeted mAbs reduce acute lung attacks and improve health status and symptom control in asthma [1–3] and these medicines are now available for the treatment of eosinophilic severe asthma in many countries [1]. Assessing treatment response to mAbs currently relies on symptom improvement and oral corticosteroid steroid (OCS) dose reduction, rather than objective methods that precisely quantify treatment response. To be eligible for ongoing anti-interleukin (IL) 5 therapy through the Australian Government's Pharmaceutical Benefits Scheme (PBS), a patient must demonstrate an improvement in the Asthma Control Questionnaire (ACQ)

[4] of at least of 0.5 units or a 25% reduction of maintenance OCS dosage without deterioration in ACQ [5].

Precision medicine using biologics offers improved treatment efficacy and efficiency [6]. However, there is a need to balance the treatment costs against the necessity to reduce the burden from severe asthma [6]. Precision medicine could do this by selecting patients most likely to respond according to their inflammatory endotype [7]. Precision medicine could also use objective measures to determine the treatment response, as proposed by the Lancet Commission After Asthma [8].

We report a case series of severe asthma patients before and after treatment with mepolizumab, and judge their response to treatment by traditional clinical (symptoms and OCS use) and physiological measures (spirometry and exercise capacity). We also applied the novel use of an imaging

method using tomographic pulmonary scintigraphy (ventilation/perfusion (V-P) single photon emission computed tomography (SPECT)). Inhalation of Technegas was used to assess ventilation and intravenous (IV) injection of Tc-99m-macroaggregated albumin (MAA) with SPECT imaging was used to assess lung perfusion.

Case Series

The four cases described are severe asthma patients who received PBS-approved mepolizumab therapy, and their response to treatment was assessed by symptoms (ACQ) and OCS requirements, as well as physiological measures including spirometry and exercise capacity measured by the 6-min walk (6MW) test. All cases also underwent V-P SPECT with Technegas (Cyclomedica, Australia) and Tc-99m-MAA before and after treatment to assess lung ventilation and perfusion. To measure ventilation, patients inhaled the aerosolized Tc-99m Technegas agent until a count rate of 1000 counts/sec was achieved. This was attained with two to three strong inhaled tidal breaths. To assess perfusion, an IV injection up to 150 MBq of Tc-99m-MMA was administered. An initial review of the imaging was conducted to ensure a sufficient pulmonary dose (not extravasated in arm). SPECT imaging was performed over approximately 8 min from a Siemen's Dual-Head Gamma Camera (Siemens Healthcare, Germany).

V-P SPECT is a nuclear medicine investigation that gives a three-dimensional functional map of ventilation and perfusion of the lungs and shows how these are affected by disease. It has widespread clinical use for the diagnosis and follow-up of pulmonary embolism. The introduction of ultra-fine aerosols, such as Technegas, has expanded the field of application for V-P SPECT. Semi-quantitative analysis of the scans was performed by a nuclear medicine physician (MB) blinded to other clinical data and according to the methods described by Bajc et al. [9] Using this method, ventilation is normalized to perfusion counts, and then the V-P quotient images are calculated. Using this protocol, attenuation correction is not required [10,11]. An overview of ventilation and perfusion in coronal and sagittal slices is useful for quality control and fast orientation regarding pulmonary pathology. Matched images are presented so that ventilation and perfusion are carefully aligned to each other. Proper alignment is also a prerequisite for V-P quotient images.

Semi-quantification of ventilation and perfusion was made by counting regions corresponding to segments or subsegments showing complete or relative mismatch, and expressing this figure in percentage of the total lung parenchyma. A segmental reduction or a sub-segmental total deficiency of function was attributed one point, and

segmental total deficiency two points. Each lung comprises nine segments, representing 18 points. Mismatch defects were expressed as mismatch points, which after division by 36 give the percentage of the lung that is affected. Thus, a theoretical total loss of lung function would yield 36 points.

All cases received between 16 and 20 weeks of mepolizumab treatment. Patients who met the PBS responder criteria were included in this case series.

The cases included were recruited from the John Hunter Hospital Severe Asthma Clinic as part of a before-after clinical study (ACTRN12617001275358). The study was approved by the Hunter New England Human Research Ethics Committee (16/12/14/4.02). Participants provided written informed consent.

Case 1

A 69-year-old female was presented with severe asthma and a history of 12 exacerbations during the 12 months prior to baseline. All required treatment with OCS. She reported breathlessness, despite maximal inhaled corticosteroid (ICS) therapy and maintenance prednisone 5 mg/day. Spirometry at baseline showed airflow limitation. Her baseline ACQ5 score was 3.0 units, indicating poor asthma control (Table 1). Baseline V-P SPECT showed uneven distribution of ventilation and perfusion with peripheral defects, retaining preserved lung function as 55%.

During the 16-week treatment period, she reported only one exacerbation. Her ACQ remained stable and she ceased the need for maintenance OCS. Bilateral improvements in ventilation and perfusion distribution were indicated by V-P SPECT including an improvement of 15% in total preserved lung function. This case shows a positive clinical response to mepolizumab and a positive response based on imaging.

Case 2

An 80-year-old male was presented with severe asthma and co-existing chronic obstructive pulmonary disease (COPD). Spirometry demonstrated persistent airflow limitation. He had poorly controlled asthma symptoms and had experienced four exacerbations in the 12 months prior (Table 1). V-P SPECT showed general uneven distribution of ventilation and perfusion with areas of absent or reduced ventilation and perfusion and some deposition of aerosol in the small airways. A total preserved imaging lung function was calculated as 50%.

Following mepolizumab treatment for 20 weeks, his ACQ5 improved and there was a marked improvement in forced vital capacity (FVC) of 1.4 L (49%) (Table 1). Some improvement in ventilation and perfusion and less

Table 1. Demographic characteristics and clinical outcomes.

Demographics	Patient 1		Patient 2		Patient 3		Patient 4	
Age (years)	69		80		29		71	
Sex	Female		Male		Female		Male	
BMI (kg/m ²)	32		36		20		25	
Smoking history (pack-years)	0		75		0		0	
Exacerbation rate*	12		4		12		6	
Hospitalization rate*	0		0		4		0	
OCS use	12		4		6		6	
Antibiotic use	3		4		6		0	
Outcomes	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Post-B ₂ FEV ₁ (L)	1.44	1.57	1.39	1.55	2.75	2.86	2.04	2.09
Post-B ₂ FVC (L)	1.96	2.2	2.83	4.23	2.81	2.93	3.82	3.91
Post-B ₂ FEV ₁ (% predicted)	68.9	75.1	53.5	59.9	89.6	92.3	69.6	71.5
Post-B ₂ FVC (% predicted)	73.1	82.1	81.1	121.6	81.0	84.0	99.0	101.6
FER	0.73	0.71	0.49	0.37	0.98	0.98	0.53	0.53
Blood eosinophils	0.58	0.16	0.64	0.04	0.82	0.04	0.80	0.19
OCS daily dose (mg)	5	0	0	0	0	0	15	8
6MWD (m)	332.8	353.8	325	310	505	456	618.3	593.5
ACQ5	3	3.2	3.4	2.6	2.6	0.6	2	0.5
SGRQ (total)	83.3	70.8	61.3	49.7	39.4	3.8	30.2	14.9
Preserved lung function (%)	55	70	50	60	75	95	45	45

*Rates measured per 12-month period prior to baseline visit.

6MWD, 6-min walk distance; ACQ, Asthma Control Questionnaire; BMI, body mass index; FER, forced expiratory ratio; FEV₁, forced expired volume in 1 sec; FVC, forced vital capacity; OCS, oral corticosteroid; SGRQ, St. George Respiratory Questionnaire.

deposition in large airways were identified at the follow-up V-P SPECT. An increase of 10% in total preserved lung function was observed. This case shows concordant clinical, physiological, and imaging responses.

Case 3

A 29-year-old female was presented with normal spirometry values, 89.6% predicted forced expired volume in 1 sec (FEV₁), and 81% predicted FVC, but monthly exacerbations leading up to the baseline visit, four requiring hospitalization (Table 1). An ACQ5 score of 2.6 units indicated uncontrolled asthma. V-P SPECT showed uneven ventilation and perfusion bilaterally. Specifically, the right lung showed a decrease in ventilation and perfusion in the upper lobe posterior and in the left lung reduced ventilation was seen in the posterior part of both upper and lower lobes. Overall, total preserved baseline function of the lung was 75%.

Following a 16-week mepolizumab treatment trial, she reported a significant improvement in asthma control with a 2.0-unit ACQ5 improvement. Her spirometry showed minor improvements. She did not report further exacerbations during this period (Table 1). The follow-up V-P

SPECT scan showed an improvement in ventilation by 20% (Figure 1). This case shows concordant clinical, physiological, and imaging responses.

Case 4

A 71-year-old male with persistent airflow limitation and poorly controlled severe asthma with an ACQ5 of 2, frequent exacerbations (six in the past 12 months), and requirements for maintenance OCS at a dose of 15 mg/day. Imaging suggested dominant changes in perfusion, particularly in the right lung. The calculated total preserved lung at baseline was 45%.

Following a 16-week treatment trial of mepolizumab, clinical improvements were demonstrated with a 1.5-unit reduction in ACQ5 (Table 1) and a reduction in prednisone from 15 to 8 mg. However, spirometry values were largely unchanged. The follow-up V-P SPECT indicated no significant difference compared to baseline and the total preserved lung function remained the same. This case shows symptomatic improvement without change to objective physiological and imaging measurements.

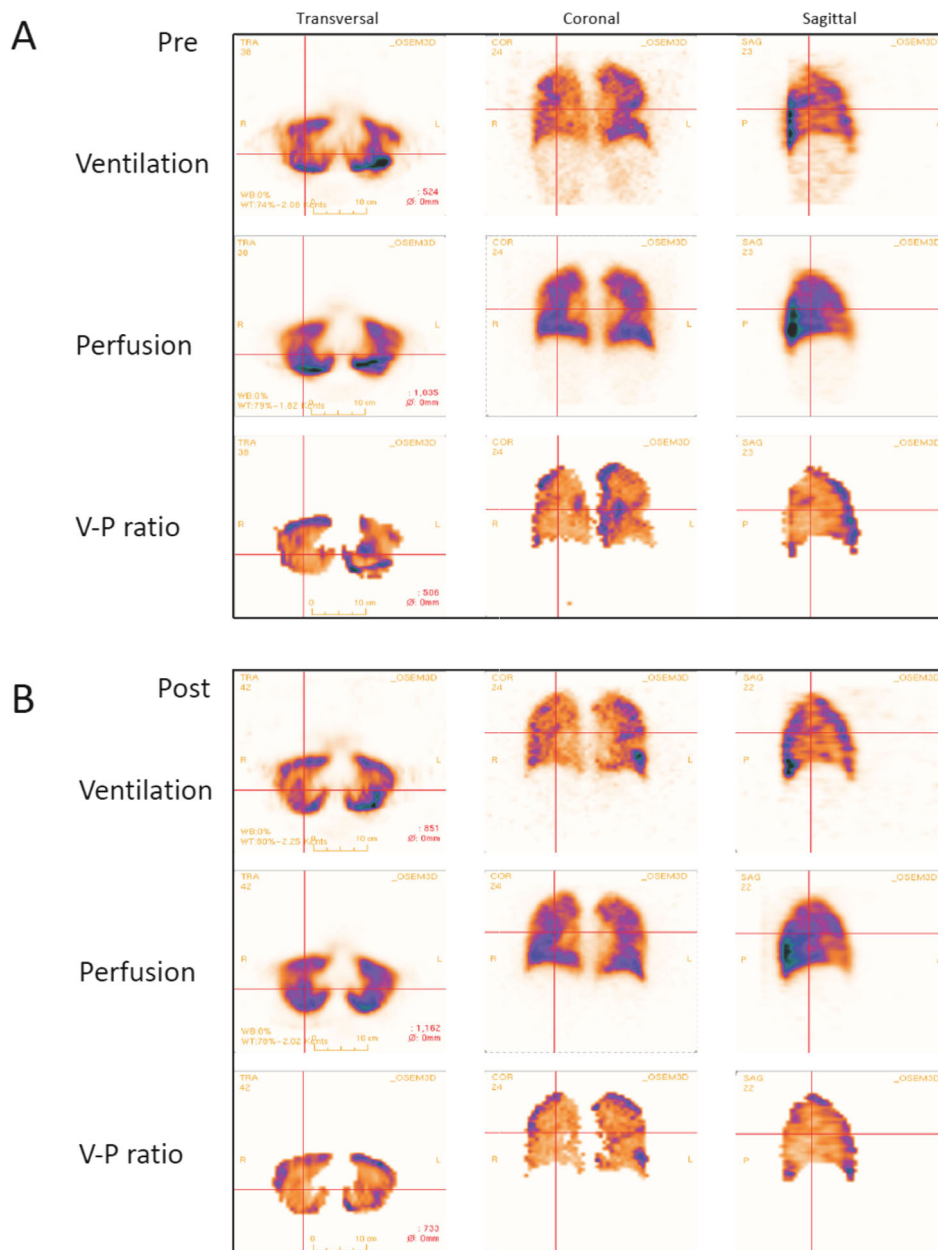


Figure 1. (A) Pre-ventilation, perfusion, and ventilation/perfusion (V-P) ratio images of reconstructed transversal, coronal, and sagittal slices from case 3. (B) Post-ventilation, perfusion, and V-P ratio images of reconstructed transversal, coronal, and sagittal slices from case 3. The images were displayed using an inverse warm metal six-step colour look up table where white represents zero/no concentration of radioactivity (V-P) and areas of purple/black represent the highest concentration of radioactivity (V-P). The intensity of the scale is targeted to visualize the apex of the lungs. The segmental chart was used to assess changes of V and P activity in the segments.

Discussion

We present four cases of severe eosinophilic asthma with a positive symptom response to mepolizumab, and demonstrate how V-P SPECT imaging may provide an objective measure of treatment effect. Case 1 ceased maintenance OCS and had improved 6MW distance (6MWD) and spirometry. Objective assessment by V-P SPECT improved demonstrating concordance with clinical assessments. Case 2 showed marked symptom and lung function improvement, consistent with improvement in preserved lung function as assessed by V-P SPECT. Case 3 also had marked symptom improvement but small lung function

changes and worse 6MWD. However, in this case, there was improvement in total lung ventilation as assessed by V-P SPECT. Finally, case 4 demonstrated an ACQ improvement and OCS reduction. However, there was no evidence of change from a physiological perspective, nor was this evident from V-P SPECT.

These changes demonstrate the heterogeneous treatment responses using clinical and physiological outcomes. We have further characterized these patients using an imaging technique, V-P SPECT, in an attempt to provide improved precision in the assessment of treatment response. The cases we present all had a positive response to mepolizumab, but

to varying degrees. Some had large improvements in symptoms with reduced requirements for OCS without physiological improvements measured by spirometry and 6MWD, while in others both clinical and physiological measures improved. In all but one case (case 4), the treatment response measured by symptoms and spirometry was consistent with improvements noted in the semi-quantitative reporting of the V-P SPECT.

Other studies have used modalities to assess ventilation in patients prescribed mAb therapies. Svenningsen et al. [12] conducted a study using inhaled hyperpolarized gas magnetic resonance imaging (MRI) to assess changes in ventilation defect percent (VDP) as a consequence of intraluminal eosinophil clearance following treatment with a T2 therapy. In 10 OCS patients with severe asthma, MRI VDP improved after treatment with anti-T2 therapy. The largest improvement was seen for patients with higher baseline eosinophil counts. This study demonstrates the sensitivity of another imaging technique (functional MRI) to anti-T2 treatments [12].

Farah et al. [13] assessed ventilation inhomogeneity in 20 adults with severe eosinophilic asthma, using multiple-breath nitrogen washout to measure global (lung clearance index (LCI)) and regional ventilation inhomogeneity in acinar (Sacin) and conducting (Scond) airways. They report significant improvements in small airway function following mepolizumab. These improvements occurred within four weeks of treatment, and consistent with our case series improvements correlated with patient symptom scores. These studies suggest ventilation measures may be useful in assessing response to novel add on therapies in severe asthma.

The data presented in the cases herein are of interest as we describe the potential use of an objective assessment that goes beyond FEV₁ in assessing response to mepolizumab. Further investigations with these techniques and qualitative analysis of the images are needed to determine whether V-P SPECT can add further precision in the assessment of patients likely to respond to biologic treatments, and in the assessment of treatment response.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case series and accompanying images.

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