



Mepolizumab improves small airway function in severe eosinophilic asthma

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ARTICLE INFO

Keywords:

Asthma
Interleukin-5
Nitrogen washout test
Small airways
Ventilation heterogeneity

ABSTRACT

Background and objective: Treatment with mepolizumab in severe eosinophilic asthma (SEA) significantly reduces exacerbations with modest improvements in symptom control and spirometry. The time course of any changes in small airway function is unknown.

Objective: To describe changes in ventilation inhomogeneity, a marker of small airway function, after commencing mepolizumab.

Methods: Prospective cohort of 20 adults (12 male) with SEA commencing monthly mepolizumab. Measurements at baseline, Week 4 and Week 26 included the Asthma Control Questionnaire (ACQ-5), spirometry, fraction of exhaled nitric oxide (FeNO) and multiple breath nitrogen washout to measure global (Lung Clearance Index, [LCI]) and regional ventilation inhomogeneity in acinar (Sacin) and conducting (Scond) airways. Other asthma therapy remained unchanged between baseline and Week 4. Treatment related changes were assessed using RM-ANOVA and paired t-tests. Relationships between changes in lung function and symptoms were assessed by Pearson's correlation.

Results: At Week 4, ACQ-5, spirometry, LCI and Sacin improved significantly ($p < 0.04$) and all were sustained at Week 26. The change in ACQ-5 correlated with the change in Sacin ($r = 0.48$, $p = 0.03$) and FRC ($r = 0.46$, $p = 0.04$), but not spirometry.

Conclusion: Improved symptom control improved rapidly after commencing mepolizumab in patients with SEA. The early improvement in small airway function was associated with asthma control and may be a significant contributor to the therapeutic response.

1. Introduction

Asthma is characterised by episodic symptoms including variable airflow limitation, with or without airway hyperresponsiveness and inflammation. The control of eosinophilic airway inflammation is important in reducing the frequency of exacerbation rates in those with moderate to severe disease [1]. Mepolizumab is a humanised anti-IL5 monoclonal antibody, which selectively inhibits eosinophilic inflammation [2,3] that is approved for the treatment of severe eosinophilic asthma (SEA). In clinical trials, treatment with mepolizumab reduces exacerbation rates by almost a half [4,5] along with modest improvements in symptom scores and forced expiratory volume in 1 s (FEV₁) [5]. In these studies, primary outcomes were reported at six month but there were apparent improvements after the first month of commencing mepolizumab treatment. The apparent discrepancy

between major patient-reported outcomes and lung function has not been explored.

The importance of the small airways in asthma has been well documented [6–8]. Eosinophilic inflammation in the small airways of patients with severe asthma [9] is considered to be an important marker of disease severity [7]. It is well recognised that spirometry is insensitive to small airway changes since it measures bulk flow propagating predominantly from the larger central airways. Abnormal small airway function causes inhomogeneity of ventilation in the lung and this can be measured using the multiple breath nitrogen washout test (MBNW) [10]. Previous studies have shown these measures of ventilation inhomogeneity relate to patient symptoms [11] as well as predict the symptomatic response to inhaled corticosteroid (ICS) dose titration [6]. The magnitude of abnormality measured with the MBNW test is worse in severe disease [12] and following asthma exacerbations

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<https://doi.org/10.1016/j.rmed.2019.01.016>

Received 22 November 2018; Received in revised form 19 January 2019; Accepted 22 January 2019

Available online 01 February 2019

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Abbreviations

ACQ-5	5-item Asthma Control Questionnaire
F _e NO	fraction of exhaled nitric oxide measured at 50 ml s ⁻¹
FEV ₁	forced expiratory volume in 1 s
FVC	forced vital capacity
FEV ₁ /FVC	forced expiratory volume in 1 s as a percentage of forced vital capacity

MBNW	multiple breath nitrogen washout
ppb	parts per billion
Sacin	ventilation inhomogeneity in diffusion-dependent acinar airways
Scond	ventilation inhomogeneity in convection-dependent conducting airways
SEA	severe eosinophilic asthma

[13]. Thus, small airway function as measured by the MBNW may be a more sensitive measure of the therapeutic response of mepolizumab.

We hypothesized that early improvement in small airway function may be a significant contributor to the therapeutic response of anti-IL5 monoclonal antibody therapy. We sought to describe early changes in ventilation inhomogeneity using the MBNW test in patients with severe eosinophilic asthma commencing mepolizumab treatment.

2. Methods

This was a prospective, cohort study, reviewed and approved by the Sydney Local Health District Human Ethics Review Board (LNR/14/CRGH/206, NSW, Australia).

2.1. Subjects and study design

Consecutive subjects with SEA commencing mepolizumab at a hospital-based airways clinic were included. All subjects fulfilled nationally approved pre-specified criteria and were managed by a pulmonologist for at least one year prior to commencing mepolizumab. All subjects had poorly controlled asthma despite receiving high dose inhaled corticosteroids (ICS) and long acting beta-agonist (LABA) combination, and had a history of at least one severe asthma exacerbation. Subjects presented for subcutaneous mepolizumab (100 mg) injection initially (Week 0), then at four weeks (Week 4) and continued monthly treatment with reassessment at six months (Week 26). The patients did not alter their usual treatment regimen between Week 0 and Week 4. Detailed lung function tests were performed at each visit in the following order: fraction of exhaled nitric oxide (FeNO), pre-bronchodilator spirometry, post-bronchodilator spirometry then MBNW. Spirometry was performed before and after inhaled bronchodilator with 4 × 100 µg inhaled salbutamol via metered dose inhaler and spacer. All testing conducted on Week 0, Week 4 and Week 26 was included.

2.2. Measurements

2.2.1. Asthma control questionnaire

Symptom control was determined using the symptom-only 5-item asthma control questionnaire (ACQ-5). A score > 1.5 indicates poor control and an individual change > 0.5 is clinically important [14].

2.2.2. Lung function tests

2.2.2.1. Fraction of exhaled nitric oxide (FeNO). The fraction of exhaled nitric oxide (FeNO) (CLD-88sp, EcoMedics, Dürnten, Switzerland) was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [15]. Recommended cutoff values for normal FeNO levels < 25 parts per billion (ppb) and elevated FeNO > 50 ppb have been published [16].

2.2.2.2. Spirometry. Spirometry (MasterScreen Body, Jaeger, Höchberg, Germany) was performed according to ATS/ERS guidelines [17]. Predicted values were derived from the Global Lung Initiative [18].

2.2.2.3. Multiple-breath nitrogen washout test (MBNW). MBNW

(Exhalyzer D, EcoMedics, Dürnten, Switzerland) was performed according to ERS/ATS consensus statement [11]. Measures included functional residual volume (FRC) and global (lung clearance index [LCI]) and regional indices of ventilation inhomogeneity attributed to the conducting airway zone (Scond) where gas transport predominantly occurs along a pressure gradient and the more peripheral acinar airway zone (Sacin) where gas transport occurs predominantly via diffusion. The upper limit of normal ± 95% limits of agreement for repeatability for LCI is 6.6 ± 0.1 turnover, Scond is 0.037 ± 0.026 L⁻¹ and for Sacin is 0.130 ± 0.027 L⁻¹ [19].

2.2.2.4. Analysis. The treatment effect was assessed using repeated measures ANOVA and paired t-tests. Associations between ACQ-5, spirometry, MBNW and FeNO measures were investigated using a two-tailed Pearson's correlation. Data are expressed as mean (SD) unless otherwise stated. A p value ≤ 0.05 was considered significant. Statistical advice was provided by Sydney University's medical statistician.

3. Results

3.1. Subjects

Twenty subjects (12 male) with SEA were studied. Baseline demographics are presented in Table 1. All patients were receiving LABA in addition to ICS. The most common ICS formulation was budesonide formoterol (10/20) and fluticasone propionate (8/20). Three subjects were receiving a small particle ICS formulation and their therapeutic response to mepolizumab was similar compared to the rest of the cohort. None of the subjects were current smokers and 16/20 subjects were never-smokers. The remaining four subjects had an average of 31-pack-year smoking history. Eighteen subjects returned to the clinic for review at 6 months after the initial mepolizumab injection (Week 26).

3.2. Week 4 assessment

ACQ-5 improved after the first injection when reassessed at Week 4

Table 1
Subject baseline characteristics.

Category	
No. subjects (female)	20 (8)
Age (years)	60 (16)
Height (cm)	168 (9)
BMI (kg/m ²)	29.4 (6.1)
ICS daily dose (micrograms)	1347 (536)
FEV ₁ (L)	1.56 (0.57)
FEV ₁ (% predicted)	54 (17)
FVC (L)	2.99 (0.80)
FVC (% predicted)	82 (16)
FEV ₁ /FVC (%)	52 (13)
Eosinophil count (x10 ⁹ /L)	0.68 (0.41)

Data are mean (SD) unless otherwise indicated. BMI; body mass index, ICS; inhaled corticosteroid, FEV₁; forced expiratory volume in 1 s, FVC; forced expiratory volume.

(−1.1 [0.8], $p = 0.01$) (Table 2). A significant improvement in ACQ greater than the minimal clinically important difference of 0.5 was seen in 15/20 subjects (75%).

The change in lung function parameters is presented in Table 2. FEV₁ improved by 0.24 (0.37) L and FVC by 0.24 (0.41) L, $p < 0.02$. LCI improved by 2.09 (2.68) TO, $p = 0.01$ and Sacin by 0.039 (0.079) L^{−1}, $p = 0.04$. There was no change in FeNO, FRC or Scnd. At 4 weeks after the first mepolizumab injection, 40% of subjects had a clinically significant improvement in FEV₁ and 60% of subject demonstrated a clinically significant improvement in LCI.

The change in ACQ-5 from Week 0 to Week 4 correlated with the change in Sacin ($r = 0.48$ $p = 0.03$) and FRC ($r = 0.46$, $p = 0.04$) (Fig. 1) but not spirometry (FEV₁ $r = -0.36$, $p = 0.12$).

3.3. Week 26 assessment

Six-month follow-up data were available for eighteen subjects. The initial changes in asthma control and lung function measures seen at Week 4 were sustained at Week 26 ($p > 0.18$) (Table 2). Fig. 2 shows the treatment effect across visits for ACQ-5, FEV₁, LCI and Sacin.

4. Discussion

This is the first study to show an improvement in small airway function following the initiation of anti-IL-5 treatment with mepolizumab in severe eosinophilic asthma. Furthermore, the improvement in small airway function, as measured by ventilation inhomogeneity, was seen rapidly after the first mepolizumab injection and was associated with a sustained response in the majority of patients. Finally, the improvement recorded in small airway function but not spirometry correlated with the improvement in reported symptoms as early as four weeks.

The results from this study provide clinically important information about asthma pathophysiology in that small airway function improved after the initiation of systemic treatment aimed specifically at targeting eosinophilic inflammation and without altering the background inhaled therapies in the first month. Previous studies have reported pathological and radiological abnormalities in the small airways of patients with asthma [8,20]. More intense eosinophilic inflammation in biopsies of small airways has been associated with more severe disease [12]. Studies have reported abnormal small airway function in severe asthma that persists despite bronchodilators and improves, but does not normalize, with small particle ICS therapy [6,12,13]. Consistent with the previous studies, the acinar airway function in this study improved but did not normalize for most patients. Since the MBNW measurement was performed post-bronchodilation, the reported improved small airway function is likely to reflect reduction in mucus and/or reduced wall oedema in the distal airway zone. The current novel results also suggest that biologic therapy might be effective because of its systemic delivery which might access the small airways in subjects with severe asthma.

Although the dose-response to inhaled corticosteroids in the small airways is unknown, inhaled delivery might be insufficient in severe asthma, where a larger dose might be needed.

Improved symptom control was seen as early as four weeks after commencing mepolizumab in these patients with severe eosinophilic asthma. Concurrent improvements in measures of lung inhomogeneity and spirometry were seen, however only the change in acinar airway function correlated with symptom control. The improvement in both FEV₁ and FVC is similar to the findings in the MENSA study [21]. This supports the notion that the distal airway compartment, and not simply proximal airway caliber, is contributing to the improvement seen in FEV₁. It is known that FEV₁ measures bulk flow and hence is insensitive to the function of the smaller airways. Physiologically, small airway dysfunction has been reported in mild and severe asthma and measured indirectly using several methods such as gas trapping, mid expiratory flow rates, oscillometry as well as measuring ventilation inhomogeneity using the inert gas washout technique. In particular, oscillometry methods such as the forced oscillation technique (FOT) and impulse oscillometry system (IOS) measure the impedance of the whole respiratory system during tidal breathing and provide information about airway caliber and heterogeneous bronchoconstriction. These tests require minimal patient effort and have been studied extensively in airways disease [22,23]. In a previous study of patients with less severe asthma, we found that MBNW parameters, but not FOT, correlated with symptom scores [6] and predicted the symptomatic response to ICS dose titration [11]. However, measuring oscillometry longitudinally in the clinic or at home [24] may be helpful in monitoring patients with severe asthma when they commence biologic agents. MBNW parameters have also been shown to improve as patients recover from severe asthma exacerbations [13]. In this current study with severe asthma, we show again that peripheral airway function assessed using MBNW is important to the perception of symptoms by demonstrating a significant correlation that was not seen with spirometry.

The current results highlight the importance of measuring lung function when managing patients with severe asthma. Current guidelines emphasize the importance of assessing symptom control as well as assessing airway function [25]. The latter is infrequently performed in clinical practice and often limited to spirometry. This is even more important in patients with severe disease suffering exacerbations. The clinical trials that demonstrated a significant reduction in exacerbation rates with anti-IL5 therapy also noted a modest, and inconsistently significant, improvement in FEV₁ [5]. Such apparent discrepancy is often viewed as a limitation of spirometry but the current study shows that other lung function tests can be useful to help us understand and, potentially, guide our treatments in this patient group. This approach has been adopted in respiratory diseases such as cystic fibrosis. The recent multicenter study by Davies et al. demonstrated definite lung function improvements using the MBNW, but not with FEV₁, following targeted treatment with ivacaftor in cystic fibrosis [26]. Importantly, the treatment effect could be demonstrated with relatively lower

Table 2

Symptom scores and lung function following the commencement of mepolizumab in 20 subjects with severe eosinophilic asthma.

Category	Week 0	Week 4	p-value (Week 0 vs 4)	Week 26*	p-value (Week 4 vs 26)
ACQ-5 (1–6)	2.8 (1.1)	1.7 (1.0)	0.01	1.3 (1.3)	0.23
FeNO (ppb)	41 (23)	48 (28)	0.05	42 (31)	0.25
FEV ₁ (L)	1.72 (0.63)	1.97 (0.73)	0.01	1.99 (0.82)	0.74
FVC (L)	3.11 (0.80)	3.35 (0.83)	0.02	3.26 (0.80)	0.86
FEV ₁ /FVC (%)	55 (14)	58 (15)	0.03	61 (18)	0.90
FRC (L)	3.33 (0.95)	3.13 (0.10)	0.20	3.27 (0.98)	0.19
LCI (TO)	12.9 (3.9)	10.8 (3.0)	0.01	11.0 (3.9)	0.58
Sacin (L ^{−1})	0.243 (0.148)	0.201 (0.099)	0.04	0.19 (0.14)	0.85
Scnd (L ^{−1})	0.063 (0.023)	0.059 (0.025)	0.28	0.05 (0.03)	0.23

Data presented as mean (SD). ACQ-5; asthma control questionnaire, FeNO; Fraction of exhaled nitric oxide, FEV₁; forced expiratory volume in 1 s, FVC; forced vital capacity, FRC; functional residual capacity, LCI; lung clearance index. *n = 18.

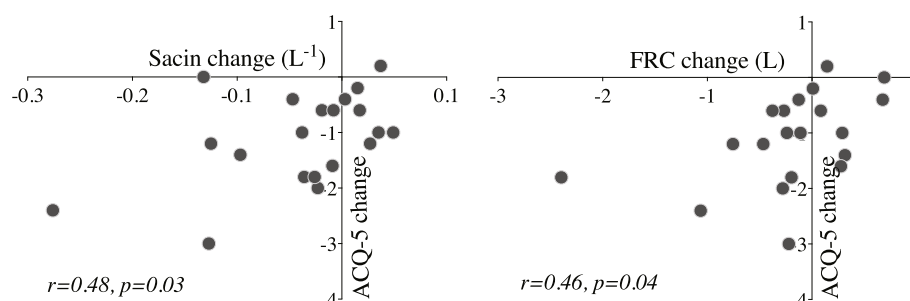


Fig. 1. Association between change in asthma control questionnaire (ACQ-5), Sacin and functional residual capacity (FRC) four weeks following initial mepolizumab (100 mg) injection in 20 patients with severe eosinophilic asthma.

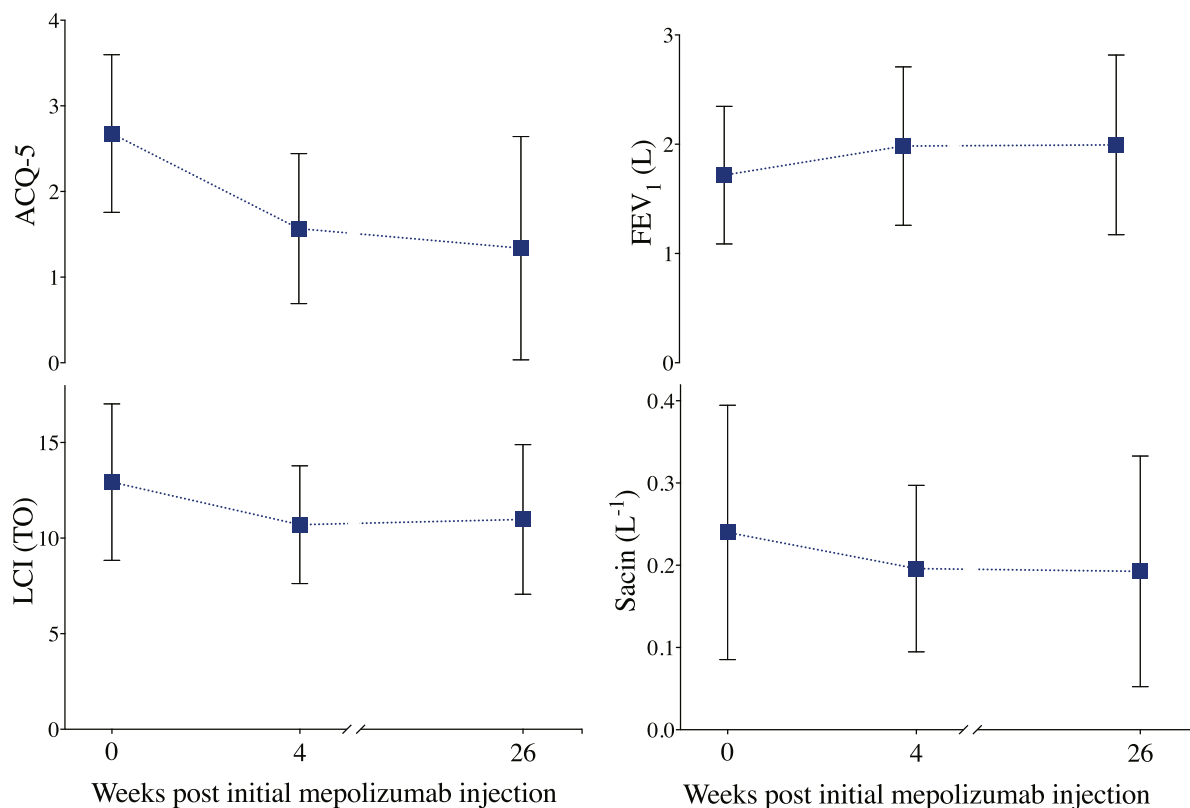


Fig. 2. Mean (SD) of Asthma Control Questionnaire (ACQ-5) scores, lung clearance index (LCI), ventilation inhomogeneity in acinar airways (Sacin) and forced expiratory volume in 1 s (FEV₁) at baseline (Week 0), one month (Week 4) and six-month review (Week 26) after commencing mepolizumab (100 mg) in subjects with severe eosinophilic asthma. RM ANOVA, $p < 0.04$ for all, $n = 18$.

patient numbers partly as a result of using such a sensitive lung function test.

The lack of any significant change in the FeNO levels following the commencement of mepolizumab treatment is consistent with published clinical trial data [4]. Indeed, FeNO remains unchanged even when mepolizumab is ceased with subsequent re-emergence of other objective markers of eosinophilic inflammation in the airways [27]. It is likely that FeNO production is not affected by the cellular targeting of mepolizumab whereas biologic agents that block other targets have reported reduction in FeNO levels in severe asthma [28]. We speculate an alternative possibility where the apparent disconnect between FeNO, measured at the single flow rate of 50 L/s, and systemic treatment targeting eosinophilic inflammation with mepolizumab might be partially explained by the relationship between small airway function and FeNO measurement. When the production of NO is partitioned into the alveolar and conductive airways by measured FeNO at different flow rates, Verbanck et al. [12] reported a correlation between alveolar NO and acinar airway function (Sacin) but no relationship between total

FeNO at 50 L/s and Sacin. The results from our study showing a reduction in Sacin would be consistent with the anti-inflammatory effects of mepolizumab occurring predominantly in the small airways, but because eosinophilic inflammation in alveolar airways is not reflected by the FeNO value (measured at 50 L/s), they would not be expected to correlate.

There are some limitations to our study. Although the sample size is small, our cohort size is comparable to previous studies where detailed lung function tests are performed to characterise a specific patient population. This was an observational study without a control group and, hence, is unable to definitively link the changes seen in small airway function to the improvement in patient symptoms. Nevertheless, the current findings are consistent with our previous work showing similar correlations in a milder group of patients with asthma. Treatment de-escalation occurred after the first month according to patient response and individual clinician practice. However, the changes reported were evident within the first month of commencing mepolizumab whilst all other therapy was unchanged, mitigating any other potential

confounders. Furthermore, the enduring improvement at six months was seen even with medication dose reduction. The individual clinicians and patients were not aware of the MBNW results, further highlighting the relevance of the reported relationship between small airway function and ACQ-5 in this study.

Our patient population differed slightly from the larger clinical trials of mepolizumab in severe asthma. At baseline, the patients in this study were older and on average had worse symptom control with higher ACQ-5 scores and lower FEV₁. A trend for an improvement in FEV₁ and ACQ-5 was noted in the MENSA trial [5] but the magnitude of change was more pronounced in the current cohort with 75% of patients reporting a significant improvement based on the ACQ-5 score. Our results raise the possibility of using a sensitive test of airway function such as MBNW to predict treatment response from the first injection. This would require a larger patient cohort with longer follow up time to adequately answer this question. Nevertheless, we speculate that the early small airway improvements noted may result in an airway tree less susceptible to catastrophic collapse and hence will relate to a reduction in exacerbation frequency as well as improved symptom scores [29].

In conclusion, we report an improvement in ventilation inhomogeneity as a marker of small airway function as early as one month after commencing mepolizumab in patients with severe eosinophilic asthma. This improvement is seen in the absence of any change to other treatments in the first month and is sustained at six months. The change in small airway function correlates with the improvement in symptom scores and may be a significant contributor to the therapeutic response.

Funding sources

Nil external funding sources.

At a glance

Mepolizumab improves small airway function after the first subcutaneous injection and this relates to the improved symptom control reported by patients. Therapies that target small airway function can improve patient outcomes.

CSF reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Mundipharma unrelated to the submitted work. GKG reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Menarini and MundiPharma unrelated to the submitted work, and grants from National Health & Medical Research Council and Asthma Australia Foundation. MJP reports personal fees from GlaxoSmithKline unrelated to the submitted work. TB, NR, PGR, CT and LMS report no conflicts of interest.

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