Protocol information

Full title:

Impulse Oscillometry Measurements in Severe Eosinophilic Asthmatics Before and After Anti-IL-5 Factor Initiation (IMPOSE)

ClinicalTrials.gov ID NCT05147155

Sponsor University of Thessaly

Information provided by Ourania Kotsiou, University of Thessaly (Responsible Party)

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Title of the trial for lay people, in easily understood, i.e., non-technical, language:

Impulse oscillometry as a method to document and monitor the efficacy of anti-IL-5 factor in patients with severe eosinophilic asthma.

SCIENTIFIC RATIONALE

Asthma is an inflammatory airways disease affecting the entire bronchial tree. The importance of small airways in asthma has been well documented [1,2]. Small airways defined as those with an internal diameter of 2 mm or less, which referred to as the silent zone of the lungs. Small airway disease (SAD) is present across patients with all stages of asthma, but it is particularly prevalent in those with more severe disease and more frequent symptoms [3]. Particularly, the silent zone has been related to asthma control, severity, and risk of exacerbation [3,4]. SAD is more prevalent in asthmatic patients with fixed airflow obstruction compared to asthmatic patients without fixed airflow obstruction [5].

The small airways contribute to the resistance in the airways of patients with obstructive airways disease [6]. It was estimated that total small airways resistance was 24% of total airway resistance in healthy adults and increased to 34% in asymptomatic newly diagnosed patients with asthma and 51% in patients with severe asthma [4].

Structural alterations at the peribronchiolar level contribute to the pathogenesis of functional abnormalities observed in patients with severe asthma [7]. Remodeling can affect small airway wall stiffness, thereby changing their distensibility [8]. An increase in type collagen, matrix metalloproteinase and fibronectin and a decrease in collagen III localized to the outer part of the lung were found in patients who died of asthma [9]. It has been recently documented that those structural abnormalities in patients with severe asthma associated with a higher frequency of exacerbations, worse asthma severity, quality of life, and asthma control [3]. Moreover, it has been reported reproducibly higher alveolar NO concentrations in refractory asthma group compared to mild-moderate asthma group, supporting the hypothesis that refractory asthma is associated with distal lung inflammation [10].

Although it is increasingly recognized that the small airways play an important role in severe asthma and SAD may complicate severe asthma treatment, it is notoriously difficult to measure small airways inflammation and/or dysfunction [11,12]. SAD is a complex and silent signature of severe asthma that is likely to be directly or indirectly captured by combinations of physiological tests, such as spirometry, body plethysmography, impulse oscillometry (IOS), and multiple breath nitrogen washout. For clinical practice, it is important to adopt easy-to-use clinical measures, such as IOS and spirometry, to delineate various severe asthma SAD subtypes.

Heterogeneous airway narrowing is a significant marker of severe asthma related to resistance and reactance [13]. IOS seemed to have better sensitivity to detect SAD than effort-dependent forced expiratory flow between 25% and 75% (FEF25-75%) [11]. Spirometry, which is the standard method for measurement of pulmonary function, is unlikely to reflect the pathophysiology of SAD since it measures bulk flow propagating predominantly from the larger central airways; therefore, there are limitations in detecting changes in small airways and airway trapping in patients with asthma [14]. Furthermore, spirometry performance remains challenging for many elderly patients who have comorbidities that affect the test procedure, as well as in cases where patient cooperation is lacking, such as children or patients with physical and cognitive limitations [14]. Therefore, a more readily available test for SAD is crucial for patient assessment.

The use of commercialized forced oscillation technique (FOT) devices to assess impedance in obstructive diseases such as asthma has gained popularity. The earlier FOT instruments allowed only one sound frequency to be passed at a time. Some of the more recent FOTs now use sound waves of two or three different frequencies at one time [15]. IOS is an improvised technique of that FOT that could use multiple sound frequencies at one time [16]. Although FOT devices are generally comparable, IOS is the most commonly used type of FOT in clinical practice [17]. IOS is a noninvasive and convenient technique to measure both airway resistance and reactance during tidal breathing by an effort-independent and patient-friendly modality for evaluating lung function and peripheral airway dysfunction [18], providing extensive description of oscillatory pressure and giving better mathematical analyses of resistance and reactance using the fast Fourier transform (FFT) technique compared to FOT. In FOT, the sound waves of different frequencies were transmitted sequentially, whereas in IOS, an impulse, which can be mathematically decomposed into different frequencies, is transmitted. This helps in reducing the time of the test and also provides a high signal to noise resolution [18]. Resistance can be conceptualized as a sound wave requires to travel through the airways and inflate the lung [19]. The reactance of the respiratory system is composed of the inert and elastic properties of the respiratory system. **The sum of the forces ahead of the sound wave (resistance) and those generated behind the sound wave in response to the pressure of the wave (reactance**) equal the impedance of the entire respiratory system; thus permits passive measurement of lung mechanics [19]. Importantly, IOS can differentiate small airway obstruction from large airway obstruction and is more sensitive than spirometry for peripheral airway disease [13,19].

The clinical classification of SAD into subtypes by use of IOS is meaningful, given its association with GINA severity stages, asthma control, quality of life, and exacerbations. IOS can be useful in determining baseline lung function, demonstrating a response to bronchodilator or bronchoprovocation, and predicting asthma exacerbations and loss of disease control especially, in children and elderly with

obstructive airway diseases [20]. Moreover, the SAD subtype classification with IOS has been used to determine the inhaled corticosteroids particle size is needed for proper airway inflammation treatment [21].

Eosinophilic inflammation in the small airways of patients with severe asthma is considered to be an important marker of disease severity [2,22,23). In clinical trials, treatment with mepolizumab reduces exacerbation rates by almost a half along with modest improvements in symptom scores and forced expiratory volume in 1 s (FEV_1) early after the first month of commencing mepolizumab treatment [23,24]. However, there is an apparent discrepancy between major patient-reported outcomes and lung function that should be explored.

It has recently been reported that mepolizumab improves small airway function in severe eosinophilic asthma as detected by multiple-breath nitrogen washout test [23]. The improvement in small airway function was seen rapidly after the first mepolizumab injection and was associated with a sustained response in the majority of patients [23]. However, gaps in knowledge about the choice of device, gas, and standardization across systems are key issues leading the committee to conclude that multiple-breath nitrogen washout test is not ready for use as a clinical trial endpoint in asthmatics [16].

In the past few months, Antonicello et al. provided data showed that FOT could be an effective method to document and monitor the efficacy of mepolizumab in treating severe eosinophilic asthma. In this study, FOT detected early treatment-induced changes in peripheral airways function [25]. This study included 18 patients with severe eosinophilic asthma, candidates for mepolizumab therapy, and no other control groups were enrolled [25]. These preliminary results motivate further prospective studies to evaluate respiratory mechanics using other FOT devices such as the IOS; thus enriching the knowledge regarding the small airway asthma phenotype by unlocking the lung's quiet zone.

HYPOTHESIS

We hypothesize that early improvement in small airway function may be a significant contributor to the therapeutic response of anti-IL-5 monoclonal antibody therapy in patients with severe uncontrolled eosinophilic asthma. We speculate that SAD could be effectively evaluated using IOS. Consequently, this study could lead to novel SAD subtypes with possible clinical relevance in the context of treatment with anti-IL-5 factor. We hypothesize that healthy individuals and patients with severe controlled asthma would disclose a lesser extent of SAD than patients with severe uncontrolled eosinophilic asthma with or without fixed airway obstruction.

OBJECTIVES

We sought to describe early changes in respiratory mechanics by means of IOS in patients with severe eosinophilic asthma commencing mepolizumab treatment. The detected parameters will be compared to a group of matched for age and gender healthy controls as well as with a group of patients with severe controlled asthma matched for age and gender requiring high dose inhaled corticosteroids (ICS) /long-acting beta-agonist (LABA) combination therapy to prevent asthma from becoming uncontrolled.

METHODS

Study Population

Our sample will consist of 40 patients between 18 and 82 years of age with uncontrolled severe eosinophilic asthma despite receiving high dose ICS/LABA combination therapy.

Principal inclusion criteria:

- Written informed consent
- Male or female outpatient aged 18 to 82 years inclusive
- History of bronchial asthma for at least six months as defined by ATS criteria [26].

  The patients will be required to have one or more of the following objective physiological criteria: positive results on methacholine or mannitol challenge during the previous year, bronchodilator reversibility to 400 mg of inhaled Salbutamol of FEV_1 ≥12% and 200ml or peak flow variability of ≥20% over two weeks.
- Diagnosis of severe asthma, defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [27, 28].

  All patients will be medicated with at least 880 μg of fluticasone propionate or the equivalent by inhalation per day and at least three months of treatment with an additional controller. Patients will be allowed to continue their anti-asthma therapy throughout the study.
- Patients should have uncontrolled asthma commencing mepolizumab treatment, based on investigator assessment, including one or both of the following:

-Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma), defined as ACQ consistently ⩾1.5 or ACT<20.

-Frequent exacerbations (≥2/year) requiring oral corticosteroids, or severe exacerbations (≥1/year) requiring hospitalization or burst of systemic corticosteroids (≥3 days) [29].

- All patients will have an eosinophil count of at least 150 cells per microliter in the peripheral blood at screening or at least 300 cells per microliter at some time during the previous year.

Control groups

Control groups will be a set of 50 healthy individuals matched for age and gender and 40 patients with severe well-controlled asthma requiring high dose ICS/LABA combination therapy from becoming uncontrolled, as previously defined, matched for age and gender.

Principal exclusion criteria:

- Diseases and health status:
  -clinically relevant abnormal laboratory values suggesting an unknown disease and requiring further clinical evaluation
  -suffering from COPD (i.e., chronic bronchitis or emphysema) and/or other relevant lung diseases causing alternating impairment in lung function
- Asthmatic patients and healthy controls currently smoking or with a smoking pack history greater than 10 will be excluded.

Common exclusion criteria:

- -pregnancy
  -intention to become pregnant during the course of the study
  -breast feeding
  -participation in another study within the 30 days preceding and during the present study
  -known or suspected non-compliance, alcohol or drug abuse
  -inability to follow the procedures of the study, e.g., due to language problems, psychological disorders

Sampling

Approximately 1000 patients with asthma per year are treated in the external Unit of Asthma of Respiratory Medicine Department of the University of Thessaly in

Greece. Nevertheless, in order to certainly achieve the estimated study sample size, to maximize the response rate and to reduce survey error, the Respiratory Medicine Department of the University of Thessaly will cooperate with a network of private respiratory physicians in Central and Northern Greece that serves a population base of about 3,000,000. Asthma education programs will regularly take place to raise severe asthma awareness, improve asthma control and management by creating a community Interlink between Respiratory Medicine Department and private sector from across central and northern Greece.

Furthermore, Respiratory Medicine Department of the University of Thessaly, via more than 12 clinical-community partnership spirometry surveillance programs with ten primary Health Care Centers in Central and Northern Greece, has already created a network of researchers, experts, and healthcare practitioners which is vitally important to early identify patients with uncontrolled asthma.

Ethics

Verbal and written informed consent will be obtained from all subjects before the study, according to the Helsinki declaration [30]. The protocol has already been approved by the Larissa University Hospital Ethics Committee (Approval number: 48841/25/10/2019)

Target enrolment/sample size: *(Required for clinical studies)*

130 (40 patients with severe uncontrolled eosinophilic asthma commencing mepolizumab treatment, 40 patients with severe controlled asthma medicating with high dose ICS/LABA combination therapy, and 50 healthy individuals matched for age and gender)

Anticipated rate of enrolment: *(Required for clinical studies)*

1 to 4 patients per month

Estimated study start date: *(FSFV/Study Start/Analysis Start)*

May 2020

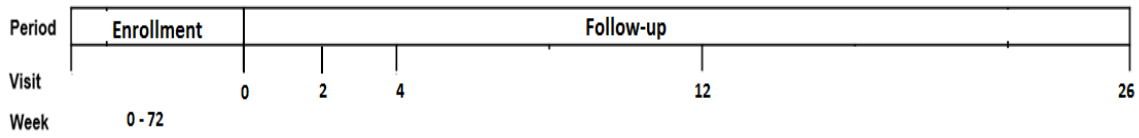
Estimated study completion date: *(LSLV/Study End/Analysis Complete)*

September 2023

Study Design and Methods

This will be a 2-year prospective, cohort study. Patients will receive mepolizumab, which will be administered as a 100-mg subcutaneous dose every four weeks. Subjects

will be present for subcutaneous mepolizumab (100 mg) injection initially at visit 0 (Week 0), then for reassessment at two (Week 2) and four weeks (Week 4) and continued monthly treatment with reassessment at three (Week 12) and six months (Week 26). The patients will not alter their usual treatment regimen between Week 0 and Week 12; thus mitigating any other potential confounder.



Detailed lung function tests will be performed at visit 0 in the following order: the fraction of exhaled nitric oxide (FeNO), IOS performance then spirometry and lung volumes measurement. All testing will be conducted before and 30 minutes after mepolizumab injection. Asthma control and quality of life questionnaires will be filled. All testing will be conducted on Week 0, Week 4, Week 12 and Week 26.

Measurements

At each clinic visit, we will evaluate the results of spirometric, IOS and lung volumes tests and will administer the 5-item Asthma Control Questionnaire (ACQ-5), Asthma Control Test (ACT), and Asthma Quality of Life Questionnaire (AQLQ).

Asthma control questionnaire (ACQ-5)

Symptom control will be 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 [31].

Asthma Control Test (ACT)

The ACT will provide us with a snapshot of how well asthma has been controlled over the last four weeks, giving a score out of 25. A score of less than 20 means that asthma may not have been controlled during the past four weeks [32].

Asthma Quality of Life Questionnaire (AQLQ)

The Asthma Quality of Life Questionnaire (AQLQ) is a 20-item self-administered questionnaire that covers four dimensions (breathlessness, mood, social limitation and worrying) and gives a total score and subscales scores. Patients have to respond to a series of statements describing how asthma (or its treatment) affects them and indicate which option closely applies to them over the past four weeks. A score of 10 corresponds to a maximum impairment of quality of life and a score of 0 corresponds to no impairment [33].

Lung function tests

Fraction of exhaled nitric oxide (FeNO).

The fraction of exhaled nitric oxide (FeNO) (MEDISOFT, MEDICAL GRAPHICS CORP, Minnesota, USA) will be performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [20]. Recommended cutoff values for normal FeNO levels < 25 parts per billion (ppb) and elevated FeNO > 50 ppb have been published [34,35].

Impulse Oscillometry (IOS)

IOS measurements will be performed in triplicate according to standard guidelines, with a Jaeger MasterScreen IOS system (Carefusion, Germany, JLAB software version 5.22.1.50) [36-38]. A volume calibration will be performed daily using a 3-L volume syringe, and the accuracy of resistance measurements will be confirmed daily using a standard 0.2 Kpa.s.L^{-1} resistance mesh. Each patient will be seated upright, wear a nose clip, and press on their cheeks with their hands to prevent an upper airway shunt. To avoid air leakage, patients will seal their lips tightly around the mouthpiece [39-41]. While the impulse will be produced by the speaker is moving with the patient's breathing, a pressure and flow transducer will be measure inspiratory and expiratory flow and pressure changes in the respiratory system. Mean values for resistance at 5 Hz (R5: indicates total airway resistance); resistance at 20 Hz (R20: approximates central airway resistance); the difference between R5 and R20 (R5-R20: considered to be an index for small airways); reactance at 5 Hz (X5: relates to compliance); resonant frequency (Fres); and integrated area of low-frequency X (AX) values will be derived as previously reported [41-44]. Fres and AX are values that detect expiratory flow limitations. R5–R20 and AX are thought to reflect changes in the quiet zone of the lungs [45]. IOS data will be carefully reviewed offline and quality-assured by professor K.I Gourgoulianis, an expert clinician, to reject segments affected by airflow leak or swallowing artifacts. Acceptability criteria for IOS measurements will include coherence values of ≥0.6 at 5 Hz, between test coefficient of variation of Zrs of <15% (with a minimum of three tests) and the absence of the following features within the flow tracings gauged by visual inspections (swallowing, glottis closure, leak around the mouthpiece, improper seal with the nose clip). The best of three acceptable attempts with the lowest respiratory resistances will be chosen for the final data analysis. During this study, one technician will obtain all IOS measurements.

Prof. Gourgoulianis make substantial contributions to the clinical application of airway diseases with more than 300 publications in this research area [46-68], performing measurements with FOT over several decades, be able to educate a number of respiratory physicians in Respiratory Medicine Department of University of Thessaly by sharing his vast expert knowledge in pulmonary physiology, FOT, and IOS testing and related areas.

Spirometry

Spirometry (Spirolab, MIR, Rome, Italy) will be performed according to ATS/ERS guidelines [69]. Predicted values will be derived from the Global Lung Initiative [70]. To avoid any negative effects of forced expiration on the airway, spirometry will never be performed before the IOS measurements. The percent predicted forced vital capacity (%FVC), the percent predicted forced expiratory volume in 1 s (%FEV_1), the FEV_1/FVC ratio, the percent predicted the maximal mid-expiratory flow (%MMEF), and the percent predicted peak expiratory flow (%PEF) would be obtained. The best of at least three technically acceptable results will be selected.

Constant volume plethysmograph

Lung volumes measurement [total lung capacity (TLC), residual volume (RV), ratio of RV/TLC], and airway resistance (Raw) will be measured in a constant volume plethysmograph (CardinalHealth, Yorba Linda, CA, USA) as previously described [71,72].

Study Endpoints

The study endpoints will be:

1) To describe early and late changes in respiratory mechanics by means of IOS in patients with severe eosinophilic asthma commencing mepolizumab treatment.

The secondary study endpoints will be:

1) To identify differences in respiratory mechanics by means of IOS in patients with severe uncontrolled eosinophilic asthma prior to anti-IL-5 therapy compared to healthy individuals.

2) To identify differences in respiratory mechanics by means of IOS in patients with severe eosinophilic asthma commencing anti-IL-5 treatment compared to patients with severe controlled asthma medicated high dose ICS/LABA combination therapy.
3) To investigate the association between RV/TLC ratio, FeNO, spirometric values and IOS measurements in patients with severe uncontrolled asthma before and after mepolizumab treatment.
4) To investigate the association between the changes in respiratory mechanics by means of IOS and asthma control measurement as defined by ACT and ACQ-

5 questionnaires in patients with severe eosinophilic asthma before and after mepolizumab treatment.

5) To investigate the association between the changes in respiratory mechanics by means of IOS and the quality of life measurement as defined by AQLQ in patients with severe eosinophilic asthma before and after mepolizumab treatment.

Statistical Plan or Data analysis

Data will be analyzed using the statistical program SPSS 22 (IBM Corporation, Armonk, NY, USA). Quantitative variables will be presented as mean with standard deviation (SD), and qualitative variables will be presented as frequencies with percentages. Chi-square test will be used to explore any associations between qualitative variables. To identify differences between two independent groups when the dependent variable will either ordinal or continuous, unpaired t-tests or Mann–Whitney U tests will be used for normally distributed and skewed data, respectively. Differences between more than two unrelated groups will be tested by one-way analysis of variance (ANOVA). A result will be considered statistically significant when the P-value will be <0.05.

Limitations

This will be the first study to investigate small airway dysfunction using IOS in patients with severe uncontrolled eosinophilic asthma commencing mepolizumab treatment. While oscillometry measurements are portrayed as a marker of small airway dysfunction, the normal reference ranges or threshold to define SAD has not been established yet. However, IOS has many advantages as is the most commonly used type of FOT in clinical practice including the use of simple tidal breathing maneuvers against forced maneuvers applied in spirometry and thus require less effort, while it demonstrates a change in early disease wherein spirometry is normal [16].

What is your planned publication? Abstract, Manuscript, Study report

- Planned Publication date (Abstract):
  January 2022

- Planned Publication date (Manuscript):

March 2022

- Planned Publication Date (Study report):
  March 2020

Planned Publication Date (**Study report**)	Planned Publication date (**Abstract**)	Planned Publication date (**Manuscript**)
March 2020	January 2022	March 2022

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