The effect of mepolizumab on patients with nasal polyp eosinophilia

Sponsor: Investigator initiated

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Summary

Study Title	The effect of mepolizumab on patients with nasal polyp eosinophilia
Objectives	Primary: 1. Assess the tissue histopathological changes in response to mepolizumab therapy in patients with nasal polyp eosinophilia Secondary: 1. Assess the effectiveness of Mepolizumab in nasal polyp eosinophilia based on patient reported outcome measures, blood eosinophilia and recorded endoscopy 2. Assess changes in serum/blood markers in response to mepolizumab therapy in patients with nasal polyp eosinophilia 3. Assess the relationship between serum/blood markers and tissue markers 4. Assess factors that may contribute to treatment failure / non-response
Study design	Phase 2 clinical trial
Planned sample size	20
Selection criteria	Adult patients with eosinophilic chronic rhinosinusitis with nasal polyposis, and who's condition is not fully managed by current standard of care Not currently receiving mepolizumab treatment. Patients who do not meet the PBS criteria for severe lower airway disease Body weight: A minimum body weight >=40 kilograms (kg) at Visit 1 Gender: Male or female. Informed consent: Capable of giving signed informed consent
Study procedures	At the initial baseline visit, prior to initiation of Mepolizumab therapy, the following set of data will be recorded: demographic data, tissue biopsy of mucosa and polyp, serum sample, smell test (threshold and identification components of the commercially available Sniffin Sticks Kit), patient reported outcome scores including SNOT-22, ACQ, smell questionnaire, FeNO and recorded endoscopy. Patients will then receive their first course of Mepolizumab therapy. They will then return every 4 weeks for routine visits for ongoing Mepolizumab provided at the clinic. There will be a tissue biopsy undertaken at every 2nd visit following initiation of therapy. In addition, there will be 4 weekly assessment of the following outcomes: blood sample, SNOT-22, ACQ, FeNo, recorded endoscopy. At visit 4, smell assessment will also be included. At the end of the 6 month treatment period, an overall assessment of treatment response / non-response would be assessed, including repeating the smell assessment. Patients will return 3 months following completion of therapy to have a post completion tissue biopsy and serum sample.

Statistical considerations	As there is limited published data regarding the effect of Mepolizumab in nasal polyp eosinophilia, sample size calculation is not available. This study is a pilot study / phase 2 clinical trial.
Study duration	5 years

1. BACKGROUND

1.1. DISEASE BACKGROUND*

Eosinophilic chronic rhinosinusitis (eCRS) is an emerging classification of chronic rhinosinusitis (CRS), thought to more accurately reflect the underlying pathophysiology. eCRS is thought to be a disease of chronic sinus inflammation rather than infection, linked with skewed T-helper 2 (TH2) allergic responses, driven by eosinophilic inflammation and a dysregulated sinus mucosa (Chin & Harvey, 2013). eCRS is diagnosed by histopathological assessment of eosinophilic infiltration within sinus tissue. There is wide variation within the literature and no consensus currently exists regarding the cut-off for diagnosis of eCRS however, an absolute eosinophil count of >10 per high power field (HPF) is generally associated with poorer outcomes and overall prognosis.

1.2. RATIONALE FOR PERFORMING THE STUDY*

Mepolizumab is an anti-IL-5 monoclonal antibody, currently used for the management of severe eosinophilic asthma and has been acclaimed as a potential treatment in the management of eCRS. The standard cut-off applied for Australian government subsidised provision of mepolizumab for eosinophilic asthma is a blood eosinophil count of $0.3x10^9$/L.

Our anecdotal experience with mepolizumab in a well defined group of chronic rhinosinusitis patients, with eosinophilic inflammation, has been very positive. We believe mepolizumab has been successful in this population due to their well defined mucosal eosinophilia, that we characterize as part of our broader clinical research program (Snidvongs et al. 2012).

We don't rely on serum eosinophil levels as a monitoring tool for sinus patients (as is done in mepolizumab for asthma) but instead use nasendoscopy. The nasal endoscopy of patients, who have had prior surgery, allows direct examination of the sinus cavity and mucosa. It is very obvious when therapy is influencing the disease, such as in corticosteroid therapy, as the mucosa often normalizes during such therapy. Such changes have been observed in patients on mepolizumab therapy.

Patients with eCRS very often suffer from smell loss, as a result of increased sinonasal concentration of eosinophils which mediate damage to olfactory epithelium and neurons (Chung et al., 2015; Wu et al., 2018; Zhang et al., 2019). Treatment with mepolizumab has been suggested to improve patient reported sense of smell (Bachert et al., 2017), however objective data has not been reported. Subjective assessments do not always correlate with functional olfaction tests, thus, the true impact of mepolizumab on smell function in eCRS is yet to be determined (Langstaff et al., 2019).

One of the challenges of defining successful mepolizumab therapy, will be demonstrating that respiratory mucosal eosinophilic inflammation decreases with treatment, and not simply the serum eosinophil level. There are many reasons why some patients may not have an immediate clinical benefit: intercurrent infection, mucosal remodelling and fixed changes, including nasal polyps in the upper airway. Remodelling changes have been demonstrated in chronic rhinosinusitis (Barham et al., 2015).

This study would provide evidence of the direct tissue response to mepolizumab, provide a relationship between tissue and serum/blood marker levels and might provide prognostic information to responders to therapy.

2. STUDY OBJECTIVES*

2.1. PRIMARY OBJECTIVE*

To identify and assess the tissue histopathological changes in response to mepolizumab therapy in patients with nasal polyp eosinophilia

2.2. SECONDARY OBJECTIVES

Assess the effectiveness of Mepolizumab in eosinophilic nasal polyp eosinophilia

Assess changes in serum/blood markers in response to mepolizumab therapy in patients with nasal polyp eosinophilia

Assess the relationship between serum/blood markers and tissue markers

Assess factors that may contribute to treatment failure / non-response to Mepolizumab

Identify a preliminary population who may benefit from Mepolizumab therapy

3. STUDY DESIGN*

3.1. DESIGN*

Phase 2 clinical trial with single group of non-blinded patients with open label therapy. At the initial baseline visit, prior to initiation of Mepolizumab therapy, the following set of data will be recorded: demographic data, tissue biopsy of mucosa and polyp, serum sample, smell test (threshold and identification components of the commercially available Sniffin Sticks Kit) patient reported outcome scores including SNOT-22, ACQ and smell questionnaire, FeNO and recorded endoscopy.

Patients will then receive their first course of Mepolizumab therapy. They will then return every 4 weeks for routine visit for ongoing Mepolizumab provided at the clinic. There will be a tissue biopsy undertaken at every 2nd visit following initiation of therapy. In addition, there will be 4 weekly assessment of the following outcomes: blood sample, SNOT-22, ACQ, FeNo, recorded endoscopy.

At the end of the 6 month treatment period, an overall assessment of treatment response / non-response would be assessed.

Patients will return 3 months following completion of therapy to have a post completion tissue biopsy and serum sample.

Each biopsy sample will be assessed and reported using a standardized synoptic histopathology profile.

3.2. STUDY GROUPS

Single group: 10 patients. Non-randomised trial. Open (masking not used)

3.3. NUMBER OF PARTICIPANTS*

10 patients

3.4. NUMBER OF SITES

Sydney Ear, Nose and Throat Clinic (67 Burton Street, Darlinghurst)

- Expected number of participants: 10

3.5. DURATION

Feb 2018 – Feb 2023. Patients will undergo 6 month treatment duration. Expected recruitment phase will be 24 months depending on ability to recruit patients to the study.

4. PARTICIPANT SECTION

4.1. INCLUSION CRITERIA*

- Adult patients with nasal polyp eosinophilia whose condition is not fully managed by current standard of care
- Not currently receiving mepolizumab treatment
- Patients who do not meet the PBS criteria for severe lower airway disease
- Body weight: A minimum body weight >=40 kilograms (kg) at Visit 1
- Gender: Male or female.
- Informed consent: Capable of giving signed written informed consent and willingness to participate to and comply with the study
- Age >18 Years

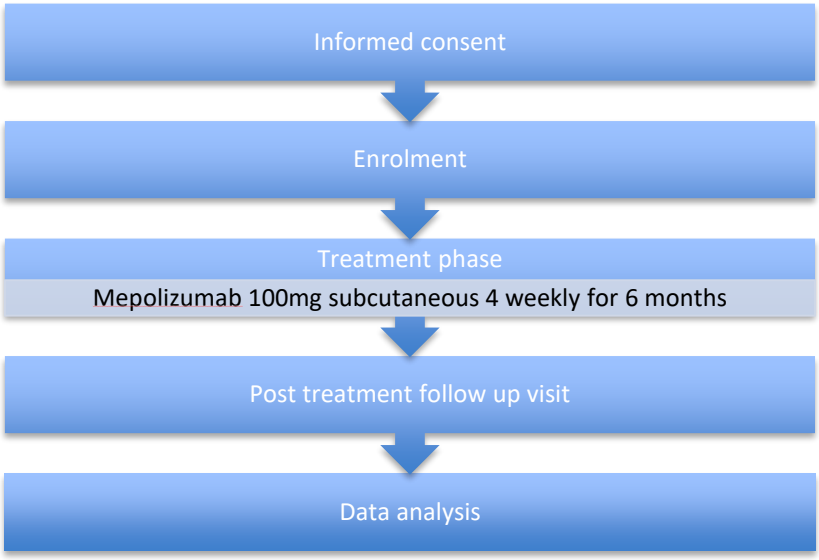
4.2. EXCLUSION CRITERIA*

- Subjects with known hypersensitivity to mepolizumab
- Subjects with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophagitis.
- Subjects with known immunodeficiency
- Subjects with cystic fibrosis
- Pregnant subjects or subjects currently lactating as the effect on human pregnancy is unknown.

5. STUDY OUTLINE*

5.1. STUDY FLOW CHART

Every patient of the investigators, who fulfils the inclusion criteria, and is undergoing assessment of chronic rhinosinusitis with nasal polyp eosinophilia, will be assessed for eligibility. Those who are eligible, willing to participate, and can provide written informed consent will be enrolled.



5.2. INVESTIGATION PLAN*

Interventions	Enrolment Visit (Visit 1)	Visit 2 (4 weeks)	Visit 3 (8 weeks)	Visit 4 (12 weeks)	Visit 5 (16 weeks)	Visit 6 (20 weeks)	Visit 7 (24 weeks)	Final Study Visit
Informed Consent	✓							
Inclusion / Exclusion criteria	✓							
Demographic Data	✓							
Questionnaires	✓	✓	✓	✓	✓	✓	✓	✓
FENO	✓	✓	✓	✓	✓	✓	✓	✓
Smell Assessment	✓			✓			✓	
Endoscopy	✓	✓	✓	✓	✓	✓	✓	✓
Blood/serum sample	✓	✓	✓	✓	✓	✓	✓	✓
Tissue biopsy	✓	✓	✓		✓		✓	✓
Adverse Event & Serious Adverse Event Assessment	✓	✓	✓	✓	✓	✓	✓	✓

Administration of Mepolizumab	✓	✓	✓	✓	✓	✓		
Overall assessment of treatment response							✓	✓

Data collection

Blood/serum samples will be obtained at a recognised pathology provider (SydPath). All other data collection / procedures will occur at the Sydney ENT clinic. Data will be collected and stored in a de-identified excel sheet which will be password protected on the co-investigator's computer.

- Patient demographic data collection: age, gender, presence of nasal polyps, past history of asthma, smoking status
- Blood/serum sample collection: venepuncture by accredited phlebotomists at a pathology provider
    - Eosinophil count, full blood count
- Recorded nasal endoscopy: a rigid nasoendoscope will be used for endoscopy following topical local anaesthetic spray.
- Tissue biopsy: performed under local anaesthetic spray and endoscopic guidance using biopsy forceps by trained individuals. The tissue will be sent to SydPath (pathology provider) for histopathological assessment and reported according to a synoptic report
- Patient questionnaires: Sino-Nasal Outcome Test (SNOT-22), Asthma Controlled Questionnaire (ACQ) and smell questionnaire (including the Individual Importance of Olfaction Questionnaire and Questionnaire for Olfactory Disorders) are validated surveys of patient reported outcome measures.
- Levels of nitric oxide were measured by NIOX VERO machine.
- Patient olfactory performance: as measured by the threshold and identification components of the Sniffin Sticks Kit (Burghart, Germany)

5.3. STUDY PROCEDURE RISKS*

Mepolizumab

- Trade name: Nucala
- Manufacturer: GlaxoSmithKline
- Supplier of drug/device: manufacturer and pharmacy
- Approved therapeutic indication: severe asthma
- Believed mode of action: Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human IL-5 with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.
- Dosage regimen: 100mg subcutaneous injection once every 4 weeks
- Mode of excretion: Mepolizumab is a humanised IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.
- Known adverse events:
    - Side effects 1 in 10: Headache.

- Side effects 1 in 100: injection site reaction (pain, skin redness, swelling, itching, and burning sensation of the skin near where the injection was given), Back Pain, Pharygitis (sore throat), Lower respiratory tract infection (congestion, cough), Nasal congestion (stuffy nose), Upper absdominal pain (stomach pain or discomfort in the upper area of the stomach), Eczema (itchy red patches on the skin), Urinary tract infection (blood in urination, painful and frequent urination, fever, pain in lower back)and Fever (high temperature).
- Side effects 1 in 10,000: Hypersensitivity (allergic reaction) including anaphylaxis (an allergic reaction that can be life threatening).

- Known contra-indications or warnings
  - Do not use if allergic to mepolizumab or any of the other ingredients of the medicine (dibasic sodium phosphate heptahydrate, sucrose, polysorbate 80)

- Blood serum collection
  - Pain at venepuncture site during collection
  - Haematoma causing discomfort and pain

- Sinus biopsy
  - Short term minimal local nasal bleeding following biopsy
  - Potential discomfort
  - Appropriate medical care will be given in the event of nasal bleeding.

5.4. Recruitment and Screening*

Patients attending the investigator's clinic at Sydney ENT Clinic will be recruited. Initial contact will be made by the investigators. Patients will be screened for the study based on their medical histories and clinical evidence of chronic rhinosinusitis with nasal polyp eosinophilia.

5.5. Informed Consent Process*

Prospective participants will be invited to read an information sheet in simple, non-technical language. This form incorporates the patient consent. Potential subjects will have up to two weeks to decide whether to take part in the study. Potential participants will have adequate opportunity to discuss the proposed trial with friends/relatives. If a patient is unable to give informed consent because of age, mental illness, dementia, communication difficulties or other reasons, they will be excluded from the study.

5.6. Enrolment Procedure*

Each participant will be enrolled into the study after screening has verified that the participant meets all the inclusion criteria and none of the exclusion criteria. Upon enrolment, the informed consent process will be completed. The participant will receive a study enrolment number and this will be documented in the participant's medical record and on all study documents.

5.7. Randomisation Procedure

N/A

6. TISSUE COLLECTION/BIOBANKING

Biopsy tissue will be collected during clinic appointments. Blood samples will be taken at accredited pathology services. Blood samples and tissue biopsies will be processed by routine pathology services

(SydPath). Tissue disposal/destruction will be as per routine pathology service protocol. Tissue will be re-identifiable.

7.SAFETY*

Adverse events are expected to be minimal. An adverse event is defined here as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the study treatment. An adverse even can therefore be any unfavourable or unintended sign, symptom or condition, and/or an observation that may or may not be related to the study treatment.

7.1. ADVERSE EVENT REPORTING*

Under the guidelines of the St Vincent's Hospital Human Research Ethics Committee, adverse events will be reported to the Committee according to the Adverse Event Reporting Policy. Adverse events related to the administration of the Mepolizumab will be reported to the Therapeutic Goods Administration and St Vincent's Hospital Human Research Ethics Committee in accordance with the requirements of the National Health and Medical Research Council, Position Statement "*Safety monitoring and reporting in clinical trials involving therapeutic goods (September 2016).*

Adverse event

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

7.2. SERIOUS ADVERSE EVENT REPORTING

Serious adverse event (SAE):
For medicines, also referred to as serious adverse drug reaction, any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

7.3. DATA SAFETY AND MONITORING BOARD

Co-investigator Raquel Alvarado has been appointed to monitor the data collection for this study. All patients will be monitored for eligibility and consent. All patients experiencing any adverse events or serious adverse event will be monitored.

7.4. EARLY TERMINATION

Should early termination of the study be necessary, for example in the case of a serious adverse event suggestive of an unacceptable benefit risk profile, the principal investigator will inform patients and the HREC.

8. BLINDING AND UNBLINDING

Unblinded study

9. OUTCOMES AND FUTURE PLANS

The plan will be for publication of project outcomes and presentation at conferences. The research will be available within the medical literature as well as in the form of a student thesis. The results from this research may form the basis of other research projects.

10. STATISTICAL CONSIDERATIONS*

As there is limited published data regarding the effect of Mepolizumab in nasal polyp eosinophilia, sample size calculation is not available. This study is a pilot study / phase 2 clinical trial. Paired T-testing would be used to identify changes following Mepolizumab therapy.
Comparative assessment of responders vs. non-responders. Assessing tissue and serum responses to changes in endoscopy and symptom scores.

11.CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS*

Consent forms will be kept in the patient files on the Sydney Ear Nose and Throat Clinic database, which is kept on a secure server with restricted access. The data custodian is Professor Richard Harvey. Patient data will be de-identified. Only the chief investigator will have access to the full data set. Data collected will be stored as an encrypted file on the co-investigator's computer.
In accordance with the NHMRC National Statement, NSW Supplement (2009), data will be retained for 15 years, at which time it will be securely destroyed.

12.OTHER STUDY DOCUMENTS

- Consent form
- eCTN study details form

13.RESOURCES

Funding/support being sought: Rhinology and Skull Base Research Group Trust Fund

14.REFERENCES*

NHMRC National Statement https://www.nhmrc.gov.au/guidelines-publications/e72?

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