Clarithromycin and endoscopic sinus surgery for adults with chronic rhinosinusitis with and without nasal polyps: study protocol for the MACRO randomised controlled trial.

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Chronic rhinosinusitis (CRS) is defined as inflammation of the lining of the nose and of the sinuses lasting longer than 12 weeks. It is a condition with a large impact on the population with a recent survey demonstrating that 11% of UK adults reporting symptoms associated with it1.

The most used medication to treat chronic rhinosinusitis is steroid sprays for the nose and a number of large studies have demonstrated this to be an effective treatment2,3. In cases where this measure has failed to manage symptoms sufficiently long-term antibiotics and surgery to open the entrances to the sinuses are commonly considered. However, there is a lack of high-quality evidence from large studies on the effectiveness of these measures4-7 and this is what the MACRO trial aims to provide. There is also some recent evidence suggesting that the use of clarithromycin (an anti-inflammatory antibiotic used in CRS) in lung disease may increase hospital admissions with heart attacks and heart failure.8

This paper aims to describe the plan for undertaking the study.

Objectives

The main objective of the study is to establish the effectiveness of a prolonged course of antibiotics and of surgery in treating chronic rhinosinusitis. The secondary aims are to evaluate the cost of the treatments, establish the frequency of side effects and to compare the effectiveness of different treatment on different sub-types of chronic rhinosinusitis.

Trial Design

The aim will be to recruit a total of 600 patients to the study, with a diagnosis of chronic rhinosinusitis in whom nasal steroids spray did not adequately treat their symptoms. The diagnosis will be based on their history, the finding of the nose examination and on a CT scan.

Each person recruited will then be randomly allocated either:

1. Intranasal medication (steroid sprays and saltwater rinses) plus sinus surgery
2. Intranasal medication plus 12 weeks of an anti-inflammatory antibiotic called clarithromycin
3. Intranasal medication plus a placebo (a medicine with no therapeutic benefit, often referred to a sugar pill)

The aim will be to have 600 participants in the study at a large number of sites around the UK.

Methods

Assessment for eligibility for the trial will be performed in the Ear nose and throat department.

Trial inclusion criteria

* Adults aged over 18 with a diagnosis of chronic rhinosinusitis (CRS) characterised as greater than 12 weeks of nasal blockage plus nasal discharge, facial pain or loss of smell.
* Nasal endoscopy (camera examination inside the nose) demonstrating evidence of CRS
* CT scan demonstrating evidence of CRS
* A score of greater than or equal to 20 on the SNOT-22 patient symptom questionnaire
* A sufficient understanding of English to be able to understand the study and provide consent for participation

Trial exclusion criteria

* More than 3 weeks continuous use of similar antibiotics to the study in the last 12 months
* Sinus surgery in the last 6 months
* Use of regular tablet steroids or biologics (a type of inti-inflammatory treatment using proteins usually produced by the body)
* Rare or complex sinus disease or sinus cancer
* Allergic fungal sinusitis
* Severe asthma on large doses of steroid inhalers
* Pregnant or breastfeeding females
* Females wanting to start a family or unwilling to use reliable contraception
* Heart disease or allergy preventing use of the antibiotic or medical conditions making surgery unsuitable
* Inability to give consent to the trial
* Enrolment in another trial in the last 4 months

Choice of antibiotic

Clarithromycin was chosen as the antibiotic for the study for a number of reasons. It has both anti-inflammatory effects and good antimicrobial properties against common bacteria to be found in the nose and sinuses9,10,11. It is also readily available and has a low side effect profile.12

Visit Schedule

After being seen in the routine clinic and informed consent taken, an ECG (heart tracing) and pregnancy test (if required) will be taken at the baseline visit. If these confirm eligibility then a comprehensive assessment will take place which includes peak expiratory flow (test of how quickly lungs can blow out air), peak nasal inspiratory flow (measure of airflow through the nose), smell assessment, routine blood tests and allergy testing (either blood tests or skin prick tests). The participants will then complete 3 self-reported symptom questionnaires (SNOTT-22, SF-12v2 and EQ-5D-5L)

Participants will be asked to complete these same questionnaires online at home at 6 weeks, 3 months and 6 months after randomisation.

Follow up clinic visits will take place at 3 months and 6 months for nasal endoscopy (intranasal camera examination), peak expiratory and peak nasal inspiratory flow.

Throughout the study period participants will be asked to complete a weekly online questionnaire from home recording their compliance with the treatment (nasal sprays and tablets)

Blinding

Participants allocated to the surgical arm of the trial will not be blinded to this (they will be made aware that they are in the surgical arm). Blinding of both trial participants and medical staff will be in place for the remaining two trial arms. That is to say that patients and medical staff will be unaware of whether they are receiving the antibiotic or the placebo to avoid any potential bias in the results.

Should a trial participant need to be treated in an emergency the participant will be ‘unblinded’ to reveal whether they were taking the active drug or not.

Otherwise participants will not be made aware of their allocation to the trial antibiotic, or the placebo.

Confidentiality

All data will be handled in accordance with the General Data Protection Regulation (EU) 2016/679. Participants joining MACRO will consent to giving identifiable information that will include their name, email address and telephone contact numbers to allow completion of the study questionnaires. If the participant does not consent to completing the documentation electronically, they will be asked instead to provide their home address and telephone number so that the MACRO trial office can send the questionnaires by post.

After randomisation each participant will be allocated a study number which will be used for identification from then on to maintain a degree of anonymisation and confidentiality.

Participant withdrawal

Participants will be able to withdraw from the study at any time. The participants do not need to give a reason for withdrawal but if they do this will be recorded. The importance of safety follow up will be emphasised to the participants. The patient will be unblinded at that point to reveal if they were taking the study antibiotic or placebo.

End of the trial

Each participant will have their final follow up at 6 months after randomisation. The trial is expected to run for 52 months. Additional funding will be sought to extend trial follow up to an additional 5 years where consent is gained.

Discussion

There is currently good evidence for the safety and effectiveness of intranasal steroids as a first line treatment in chronic rhinosinusitis. However, there is less good evidence for the safety and effectiveness of long-term antibiotics. This study aims to provide that evidence which may help to reduce unnecessary usage and therefore potential side effects. The results on the effectiveness of surgery may reduce delays to surgery (if effective) or reduce requirement for surgery if it is proven to be ineffective.

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