Feasibility study: clarithromycin for chronic rhinosinusitis

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Lay Summary:
Chronic rhinosinusitis (CRS) is a disease caused by swelling of the lining of the nose and sinuses which persists for more than 12 weeks. Symptoms include a blocked and/or runny nose, a poor sense of smell and a feeling of pressure or pain across the face. Many sufferers also report fatigue. At present, treatment includes nasal sprays and drops containing steroids, steroid tablets and antibiotics. Much of the burden of disease is managed by General Practitioners, with persistent or difficult cases referred to secondary care where they are treated with maximum medical therapy, before turning to surgical intervention to open the sinuses. However, the exact regime of treatment in both primary and secondary care can be extremely variable between practitioners and between different units across the UK.

This study will evaluate the feasibility of a double-blinded randomised controlled trial to determine the exact role of antibiotics in the management of CRS. Clarithromycin is already in widespread use for a wide range of infections and is known to be very safe. Several different measures will be used to decide whether the antibiotics work including examination of the inside of the nose, x-ray scans of the sinuses (computer tomography), smell tests and self-reported questionnaires about the participants’ symptoms. Patients recruited for the feasibility study will receive the current standard care provided at the Trust.

Following the results of the feasibility study, the double blinded randomised controlled trial will involve comparison of a 12 week course of clarithromycin (two different dosing regimens) and placebo. If either course of antibiotics is shown to treat CRS better than placebo then patients may be able to avoid having surgery, and could be treated by their family doctor instead of attending a specialist clinic in hospital. If the shorter duration
proves as effective as the longer, this will both save money and inconvenience for patients, and may avoid potential morbidity from side-effects of the antibiotics.

Summary:
As CRS is primarily a medical disease, much of it is managed by General Practitioners with those cases failing medical therapy in the community being referred to secondary care. The European Position Paper (EPOS) in 2007 set out clear guidelines for the treatment of CRS (with and without polyps) in both primary and secondary care. Whilst ENT surgeons are likely to be familiar with these guidelines, GPs are often less so. Once the patient arrives in secondary care, the clinicians typically try maximum medical therapy before turning to surgical intervention. However the exact details of treatment both in primary and secondary care can be very variable between practitioners and in different units, as indicated with surgical intervention in the 2001 UK National Sino-nasal audit. The EPOS paper has stated that evidence for the use of macrolides is currently poor and requires good quality controlled trials to better determine their place in the treatment of CRS, and this has been further augmented by a recent Cochrane review. Bacterial organisms typically found in these patients include Staphylococcus aureus, accounting for 39% of cultured samples, followed by Haemophilis influenzae (29%), Pseudomonas aeruginosa (15%), Streptococcus pneumoniae (12%). The majority (87%) of Staphylococcus aureus isolates found in this recent study were shown to be resistant to Penicillin G, as well as between 6-14% being resistant to clindamycin, cefazolin, erythromycin and cloxacillin. In this context, the resistance patterns show that the macrolides still represent the most effective antimicrobial agents for Staphylococcus aureus infections.

This study will evaluate the feasibility of a double-blinded randomised controlled trial to determine the role of antibiotics in the management of CRS. The feasibility study will be carried out at six NHS hospital (RCT proposed for nine additional centres). Total involvement of each participant will be six months for the feasibility study (nine for the RCT).

In order to determine the exact role of macrolides including, the duration of treatment, in the management of CRS, the RCT will involve a comparison of clarithromycin with a placebo as well as looking at two different dosing regimens (once daily compared with twice daily – overall dose the same). If the outcomes show clarithromycin to be effective then there may be an increased role for its use in primary care and thus avoidance of referrals to secondary care. Similarly, if the once daily preparation proves as effective as twice daily this may improve compliance and reduce side effects (nausea, vomiting, abdominal discomfort, diarrhoea (antibiotic-associated colitis); less frequently urticaria, rashes/allergic reactions; reversible hearing loss; cholestatic jaundice, pancreatitis, cardiac effects, myasthenia-like syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported; also dyspepsia, tooth and tongue discoloration, smell and taste disturbances, stomatitis, glossitis, and headache).

Introduction: The Need For a Trial

What is the problem to be addressed?
Macrolide antibiotics are currently part of the recommended medical treatment for chronic rhinosinusitis (CRS) due to their ability to cover the common organisms seen in the disease and there is some in-vitro evidence to suggest they have an anti-inflammatory effect. However the evidence to support this is poor.
What is the hypothesis to be tested?
To test the feasibility of delivering part of a multi-centre trial for clarithromycin vs placebo in CRS.

Why is a trial needed now?
The existing literature has been studied and only two randomised controlled trials (RCT) are published for roxithromycin and azithromycin. Existing management strategies vary between clinicians despite guidelines being present due to the paucity of data available, but trials with no placebo would appear to suggest that macrolides are likely to be beneficial. A feasibility study is needed to ensure the proposed trial protocol is practicable and acceptable, and to help evaluate potential recruitment to the RCT.

Has a systematic review been conducted and what were the findings?
A very recent Cochrane review confirmed that there is only 1 RCT providing level 1b evidence and concluded that further studies are needed to decide on the place of long-term antibiotics in the management of CRS.

How will the results of this trial be used?
The feasibility study will help to evaluate whether the protocol proposed for the RCT will be practicable with particular reference to the pre and post treatment evaluations and recruitment. If a significant benefit is found from the treatment arms of the RCT, there will be implications for guidelines in both primary and secondary care. Results will be disseminated through medical journals including specialty specific ones and through conferences such as the British Academic Conference in Otalaryngology and the American Academy of Otorhinolaryngology/Head & Neck Surgery Annual Conference. A negative result will prompt research for other alternative treatment modalities.

Are there any risks to participants of the feasibility study?
The study will involve the use of existing treatment strategies, but formalised in a manner so that pre and post treatment evaluation of symptoms are consistent. The subjects will therefore mainly be subjected to drugs and tests including a CT scan which would form part of routine clinical care. The drugs involved have known side-effect profiles and any adverse reactions will be monitored throughout the trial.

Methods:

What is the proposed study design?
This study would be conducted as a multi-centre study in patients undergoing standard management for CRS (without polyps). Patients with positive history and examination/CT findings would be entered into the feasibility study and a 12 week course of clarithromycin (twice daily) given. Endoscopic examination and cultures, along with symptom scores (SNOT-22 – as per normal clinical practice) would be evaluated at the beginning, and end of the trial to determine any differences.

What are the planned trial interventions?
Normal Clinical Practice at the Study Locations:

Patients would be prescribed a 12 week course of clarithromycin 250mg b.d. orally; Nasonex (mometasone) nasal spray 2 squirts b.d. both nostrils; nasal douching using a Neil Med rinse bottle and sachets b.d.

All patients referred to the participating centres and diagnosed with CRS without polyps will be offered participation in the trial provided they meet the inclusion and exclusion criteria set out below. CT scans will be performed to exclude underlying disease that may require surgery (e.g. mucocoeles) and for staging (Lund-Mackay score). Also as per normal clinical practice, patients will receive an endoscopic examination of their nose to confirm the diagnosis and to collect mucopus samples. Sinus secretion collectors (Xomed) will be used for microbiological sampling to increase diagnostic accuracy. Patients will have a skin prick test to detect allergy (routine) and a blood sample will be taken for IgE levels. All patients will also undergo saccharin tests (for mucociliary clearance) and Sniffin’ Sticks tests (for sense of smell). These are tests which have been frequently used in routine clinical practice.

The SNOT-22 questionnaire will also be used at all time points in the study as this is routinely used by all clinicians at the sites involved as part of normal practice.

At the end of the 12 weeks patients will be examined endoscopically again as is routine practice and the saccharin test and Sniffin’ Sticks test will be repeated.

Additional Assessments:

Patients will be asked to complete the SF12 and EQ-5D questionnaires at the beginning and end of the active treatment phase of the study, as well as at 3 months after the initial 12 week participation has ended. The study will assess the recruitment and retention that result from asking patients to go through these additional tests and questionnaires.

Following completion of the study, patients will continue with a normal clinical pathway: either they will be deemed free of active disease (and recommended to use nasal douching (+/- nasal steroids) as required, or persistent sufferers and offered endoscopic sinus surgery, having failed maximum medical therapy.

What is the proposed duration of the treatment period?
Participants will receive a 12 week course of the current standard treatment provided by the Trusts involved.

What are the planned inclusion/exclusion criteria?

Inclusion criteria:

- Diagnosis of chronic rhinosinusitis (without polyps) as per the criteria laid out in the European Position Paper on Sinusitis (EPOS): greater than 12 week history of nasal congestion and/or nasal discharge along with hyposmia and/or facial pressure/pain; confirmed on endoscopic findings of mucopus and/or CT scan changes
- Age – over 16 and less than 70
• Maximum medical therapy has not been tried

**Exclusion criteria:**

• Nasal polyps
• Diagnosis of allergic fungal rhinosinusitis (as per Bent & Kuhn criteria\(^\text{18}\))
• Presence of other inflammatory conditions that affect the sinonasal tract e.g. mucocoeles, Wegener’s granulomatosis, Churg-Strauss Syndrome, sarcoidosis
• Immunodeficiency states e.g. HIV, antibody deficiency, other immunocompromised state
• Children under the age of 16 and adults over the age of 70
• Contraindication to the use of clarithromycin (including: hepatic dysfunction/jaundice and renal impairment (use half normal dose if eGFR less than 30 mL/minute/1.73 m\(^2\); avoid Klaricid XL\(^\circ\) if eGFR less than 30 mL/minute/1.73 m\(^2\))

**What are the proposed outcome measures?**
The outcome measures for the feasibility:-

**Primary outcome measures:**
Number of patients recruited over time
Compliance with assessments and treatment
Time taken to perform assessments
Loss to follow up

**Secondary outcome measures:**
Patients will be asked for their feedback about their experience of participating in the study with particular reference to the pre and post treatment evaluations.

**What is the proposed frequency of follow-up?**
After commencing the trial, participants will be asked to attend a follow up visit after 12 weeks. They will then be sent questionnaires 3 months after the end of the treatment – this will assess their compliance with completion of the follow-up questionnaires.

**How will the outcome measures be assessed at follow-up?**
The outcome measures will be assessed in the same way at follow-up visits including examinations, tests and questionnaires as described above.

**What treatment will the patients receive after the feasibility study finishes?**
Patients with resolution of symptoms are advised to use nasal douching as symptoms dictate; patients with persistent symptoms/signs are offered sinus surgery. Sinus cultures will be taken as routine care if needed.

**What is the planned recruitment rate?**
At the proposed centres for the feasibility study there are estimated to be about 125 new patients per year with CRS attending the clinic. We aim to recruit over 6 months.

**Are there likely to be any problems with compliance?**
Compliance with the treatment course is likely to be affected by any side-effects experienced resulting from the clarithromycin. Any unused medications will be returned to pharmacy by the patients to help assess compliance. Any increase in symptoms may also prompt a failure of compliance in participants.
What is the likely rate of loss to follow-up?
This is anticipated to be 5-10% of participants. Those who do not attend their follow up appointment will be offered a further appointment to attend.

How many centres will be involved?
Six centres – Great Yarmouth, Guildford, Guys & St Thomas, Newcastle, Nottingham and Birmingham.

What is the proposed type of analysis?
Recruitment rates and compliance will be measured.

What is the proposed frequency of analyses?
The analysis of the trial data will be performed once only at the end of the study unless further data comes to light that requires a further analysis.

Trial Management:

What are the arrangements of the day-to-day management of the trial?
The lead investigator and a research associate (RA) will co-ordinate trial activities including recruitment and follow-up of participants in the clinic. The lead investigator will ultimately be responsible and accountable for the patients under their care and the RA will report to them. All data will be coded anonymously, kept in a password encrypted file and stored in accordance with UK data protection regulations.

What will be the responsibilities of the applicants?
Mr Carl Philpott – Chief Investigator and overall trial co-ordinator.

Who is the trial statistician?
Dr Allan Clark, Senior Lecturer in Medical Statistics at UEA.
References:


Appendix

Flow chart of trial progression (feasibility study)

50 patients with CRS recruited from the outpatient clinic when referred from primary care

CT scan performed; Nasal endoscopy, saccharin test, skin prick test (SPT), Sniffin’ Sticks (approx 80mins for all) SNOT-22, SF-12, EQ-5D questionnaires completed

Patients receive 12 weeks of clarithromycin 250mg bd plus Nasonex and nasal douching bd

Patients with resolution of symptoms are advised to use nasal douching as symptoms dictate; patients with persistent symptoms/signs are offered sinus surgery. Sinus cultures will be taken as routine care if needed.

Endoscopy, saccharin test and Sniffin’ Sticks tests repeated

SNOT-22, SF12 and EQ-5D repeated

Follow up at 3 months via application of SNOT-22, SF12 and EQ-5D in the post. Repeat clinic visit if deemed clinically necessary.