PROTOCOL OUTLINE AND GUIDELINES

Identifiers: NCT02927834 Unique Protocol ID: 5130196

Brief Title: Oral Steroids in Chronic Rhinosinusitis Without Nasal Polyps

Investigators must submit well-organized, detailed information about the study, demonstrating sound research design that minimizes risks to the subject. PI should assure that the content outlined below is addressed and may exercise some discretion as to how the information is organized. The quality and content of the protocol should demonstrate that scientific and merit review of the study has occurred at the departmental level prior to submission to the IRB.

1. PROTOCOL INFORMATION

Title: Efficacy of broad spectrum antibiotics combined with oral steroids versus antibiotics alone in the treatment of chronic rhinosinusitis (CRS) in adults without nasal polyposis (CRSsNP)

Funding Source: None.

Phase of Study: Phase 4

Version Date of Protocol: 12/3/2020

2. PRINCIPAL INVESTIGATOR'S INFORMATION

Kristin Seiberling, MD. Loma Linda University Department of Otolaryngology Head and Neck Surgery, 11234 Anderson Street, Loma Linda CA 92354. Ext 2260, fax 44819

3. STUDY PERSONNEL

Kristin Seiberling, MD – PI

Christopher Church, MD – Co-investigator

Christopher Vuong, MD – Resident investigator

4. STUDY INFORMATION

Location(s) of Research Activity: Loma Linda Sinus and Allergy Center

Expected Start/Stop Dates of Research: Start upon IRB approval, will plan to conduct study and collect data over 12 months

Special Time Sensitivities: None

Type of Research: Interventional

5. INCLUSION / EXCLUSION CRITERIA

Inclusion Criteria:

1. They have three-months of persistent symptoms meeting criteria for chronic rhinosinusits as defined by the Taskforce on Rhinosinusitis.

2. They have a CT-scan in our clinic or have a viewable recent (< 3weeks prior to clinic visit) CT-scan with a Lund Mckay score of 6 or greater. A Lund Mckay score of 6 or greater is felt to be indicative of at least moderate CRS.

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3. They do not have nasal polyps on initial clinic nasal endoscopy

4. They are willing to participate in a clinical study

5. They are between the ages of 18 to 80.

Exclusion Criteria:

1. They have a condition in which the use of systemic corticosteroids is contraindicated such as diabetes will be excluded.

2. They are unable to or unwilling to take the prescribed antibiotics or steroids will excluded.

3. They have been treated with a > 3 week course of antibiotics and/or systemic steroids will also be excluded.

4. They have variants of chronic sinusitis known to be refractory to medical therapy such as Wegener's granulomatosis, primary ciliary dyskinesia or sarcoidosis.

5. They have sinusitis secondary to prior surgery, a dental procedure or anatomical variants.

6. They have nasal polyps on physical exam.

7. They are pregnant. Subjects who are possibly pregnant will be excluded based on history. Pregnancy testing is not standard of care for diagnostic imaging.

8. They have a Lund-Mckay score on CT scan of < 6

9. They are < 18 or > 80 years old

6. SUBJECT RECRUITMENT & SCREENING

Number of Subjects: ~40

Subject Age Range: ≥18 years of age, ≤80 years of age

Subject Gender: Both

Racial/Ethnic Distribution: Any

Target Study Population: Patients without nasal polyps who suffer from chronic rhinosinusitis.

English/Non-English Speaking Subject Info: Translators will be provided for non-English speaking patients

Certified Translated Consent Form Use: None

Recruitment Material Type Info: All patients who present to Loma Linda Sinus and Allergy center meeting inclusion criteria will be asked to participate

Vulnerable Subject Info: N/A

Recruitment Method Info: Patients without nasal polyps as documented by endoscopy and who are not currently taking antibiotics or nasal/oral corticosteroids will be prospectively recruited. This will be a randomized blinded study. Patients will be randomized into three groups- Group 1 will received oral antibiotics (Bactrim or Augmentin) nasal steroid sprays (fluticasone) along with nasal saline irrigation , Group 2 will receive oral antibiotics, steroid nasal spray and in addition oral steroids (prednisone) at a tapered dosage for 6 days, and Group 3 will receive oral antibiotics, steroid nasal spray and in addition oral steroids at a tapered dosage for 20 days. The investigator will be blinded as to which group the subjects are placed.

Description of consent precautions regarding subject rights and welfare: Informed consent will be obtained from all patients after they have been given the opportunity to have their questions answered.

Pregnancy Status Info: Pregnant patients will not be included in study

7. INFORMED CONSENT PROCESS

Specific description of informed consent process: Informed consent will be obtained from all participating subjects prior to enrollment in the study. (See attached informed consent form) The risks, benefits and alternatives will be discussed with potential subjects by clinic investigators listed above (Drs. Seiberling, Church and Vuong) at time of appointment at Loma Linda Sinus and Allergy center. Patient information will be kept private and there will be time for decision-making/discussion prior to enrollment in the study. Patient who are able to verbalize/demonstrate their understanding and are able to give informed consent will be considered. Subjects will be identified by state ID or Driver's license and will be randomized into one of two study groups by flip of a coin.

Coding system: diagnosis and office visits will be coded in the standard fashion.

Privacy of Medical and Research Records information/medical records: Patient information and study data will be kept as hard copy by PI in locked desk/room and some study data will be kept on encrypted/protected flash drive by PI.

Medical Release forms, HIPAA compliance/authorization form: See attached form

8. STUDY DESIGN

a. Background or rationale for this study: Chronic sinus infections (chronic sinusitis or CRS) are common conditions that affect millions of Americans. This disease can be divided into two main patient groups: Patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and those with nasal polyps (CRSwNP). We will be focusing on the non-polyp group. While this is a common disorder, medical treatments for this condition vary considerably and little is known how and why different treatments work in some individuals and not in others. Topical nasal steroids and oral antibiotics are the mainstay and standard of care for both CRSsNP and CRSwNP. Oral steroids are commonly given for both of these sinusitis variants, however their role in non-polyp CRS patients is less well delineated. The purpose of this research study is to better

understand whether orally administered steroids results in superior results when compared with nasally sprayed steroids in this population. The investigators will compare patients with chronic sinusitis who are treated with antibiotics, topical nasal sprayed steroid therapy, and compare them to chronic sinusitis patients who receive antibiotics and nasally sprayed steroid therapy along with a short course or long course of oral steroids. The goal is to determine if oral steroids have a role in CRSsNP, and if so, the most effective dosage.

b. Objectives. *To compare the effectiveness of topical nasal steroid sprays, oral antibiotics and saline nasal irrigations versus topical nasal steroids, oral antibiotics, saline nasal irrigation + oral corticosteroids (prednisone) in CRS patients without nasal polyps.*

c. Procedures involved (Research Interventions). Chronological order of all research interventions, distinguishing standard of care vs. research intervention:

1. At the time of enrollment nasal endoscopy will be performed to confirm that the patient does not have evidence of nasal polyps. Office-based sinus CT scan will also be completed on initial visit. Lund-McKay score at initiation of treatment will be one a determinate of study eligibility. (Lund-McKay staging system is currently the most widely accepted system to radiographically characterize and diagnose CRS. A score of 6 or greater indicates significant sinus disease and meets inclusion criteria for study. See below table 1 for Lund-McKay staging system.) Note: Endoscopy and CT of paranasal sinuses are the standard of care for evaluation of patients with symptoms of CRS and will be offered to all patients presenting with these symptoms regardless of study enrollment status.

2. Subjects will be asked to fill out a SNOT 22 survey before the start of therapy.

(SNOT 20 form attached).

3. Nasal endoscopy score will also be obtained during initial visit. (Nasal endoscopy scoring form attached). This exam is part of the standard of care.

4. Subjects will be randomized into 3 groups via an electronic random generator (see below)

1. Group 1: Treated with oral antibiotics, nasal steroid spray and saline rinses for 3 weeks (standard of care)

2. Group 2: Treated with above + Prednisone 6 day tapered dosage (standard of care)

3. Group 3: Group 2: Treated with above + Prednisone 20 day tapered dosage (standard of care)

4. Random generator:

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5. Patients will return to office at 4 weeks (following 3 weeks of oral antibiotics, nasal steroid spray, nasal saline irrigation + prednisone for patients in Groups 2 and 3), At that time, patients will be asked to fill out SNOT 22 survey, nasal endoscopy and CT scan to assess response to treatment. (standard of care).

6. At the 4 week follow up, patients will be asked to fill out SNOT 22 survey, and undergo nasal endoscopy. (standard of care).

d. Alternative procedures, if any, that are not included in the study but might be advantageous to the subject - None

e. If any deception is required for validity of this study, explain why this is necessary and how subject(s) will be debriefed. - None

f. Concise review of literature that supports the rationale, objectives, and methodology of the proposed study.

1. Chronic sinus infections (chronic sinusitis or CRS) are common conditions that affect millions of Americans. This disease can be divided

into two main patient groups: Patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and those with nasal polyps (CRSwNP). We will be focusing on the non-polyp group. While this is a common disorder, medical treatments for this condition vary considerably and little is known how and why different treatments work in some individuals and not in others. Topical nasal steroids and oral antibiotics are the mainstay and standard of care for both CRSsNP and CRSwNP. Oral steroids are commonly given for both of these sinusitis variants, however their role in non-polyp CRS patients is less well delineated. The purpose of this research study is to better understand whether orally administered steroids results in superior results when compared with nasally sprayed steroids in this population, and if so, at which dosage. The investigators will compare patients with chronic sinusitis who are treated with antibiotics, topical nasal sprayed steroid therapy, and compare them to chronic sinusitis patients who receive antibiotics and nasally sprayed steroid therapy along with oral steroids. The goal is to determine if oral steroids have a role in CRSsNP. (See below for literature review.)

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g. *If an Investigational New Drug (IND) is involved, provide the following information: (1) name of drug, (2) source of drug, (3) dosage and schedule of administration, (4) status with Food and Drug Administration and IND#, (5) review of animal studies and previous human studies, (6) reported side effects.*

– Not applicable to this study

h. For an approved drug used in an experiment, provide similar information:

1. Fluticasone propionate nasal spray 400mcg qday given as 2 sprays (50mcg propionate per spray) to each nostril twice a day daily. Common side effects include: Headache. Back pain, minor nosebleed, menstrual cycle disturbance,

sinus pain, cough, sore throat, sore or white patches inside or around nose

1. Augmentin (amoxicillin/clavulanate 875/125mg) PO BID for 3 weeks. Common side effects: Diarrhea, nausea, rash, urticarial, pruritis, epigastric discomfort, vomiting, glossitis, stomatitis, candidiasis, LFT elevation

2. If allergic to Augmentin: Bactrim DS (Trimethoprim/sulfamethoxazole160/800mg) PO BID for 3 weeks. Common side effects: Nausea/vomiting, rash, diarrhea, dizziness, utricaria, headache, lethargy

3. Prednisone 6 day taper given as 30mg PO QD for 2 days, 20mg PO QD for 2 days, 10mg PO QD for 2 days, then stop. Common side effects: Fluid retention, increased sweating, headache, insomnia, nervousness, mood swings, edema, muscle weakness, BP elevation, facial erythema, menstrual irregularities, hypokalemia, intraocular pressure increase, shortness of breath, weight gain.

4. Prednisone 20 day taper given as 40mg PO QD for 5 days, 30mg PO QD for 5 days, 20mg PO QD for 5 days, 10mg PO QD for 5 days, then stop. Common side effects: Fluid retention, increased sweating, headache, insomnia, nervousness, mood swings, edema, muscle weakness, BP elevation, facial erythema, menstrual irregularities, hypokalemia, intraocular pressure increase, shortness of breath, weight gain.

5. Nasal saline ad lib

g. If an Investigational Device (ID) is involved, provide the following information: (1) name of device, (2) manufacturer, (3) status with Food and Drug Administration and ID#, (4) review of animal studies and previous human studies, (5) reported adverse effects. – Not applicable

9. DATA COLLECTION

As above. The data which will be collected is clinic nasal endoscopy score, visual analogue score (VAS), SNOT 20 score and initial CT of paranasal sinuses with Lund7

McKay score. Response to treatment as recorded by subjective scoring systems above will be recorded in hard copy and be kept by PI in secure, locked drawer.

10. LABELING & STORAGE OF DATA & SPECIMENS

Description of consent document storage/time/destroyed/disposed, research records and data storage/time/destroyed/disposed, hard copies vs. electronic, research specimens storage/time/destroyed/disposed and any special storage conditions

11. DATA ANALYSIS

Data will be compiled and statistical analysis will be made using PRISM software

12. RISK AND INJURY

This study poses minimal risk

13. BENEFIT(S)

This study will demonstrate whether or not oral steroids in addition to antibiotics and topical nasal steroids are efficacious in the treatment of CRSsNP.

14. COMPENSATION

None

15. CONFIDENTIALITY

All patient information and data will be kept confidential

16. LITERATURE REVIEW

a. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, Kette F. Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. J Allergy Clin Immunol. 2006 Jul;118(1):128-33. Epub 2006 May 19.

b. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol Head Neck Surg. 2007 Oct;137(4):555-61.

c. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009 Oct;34(5):447-54.

d. Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic

rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. Rhinology. 2001 Jun;39(2):75-9.

e. Stankiewicz JA, Chow JM. Cost analysis in the diagnosis of chronic rhinosinusitis. Am J Rhinol. 2003 May-Jun;17(3):139-42.

f. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope. 2006 Feb;116(2):189-93