INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0068 PRINCIPAL INVESTIGATOR: Steven Pavletic, MD

STUDY TITLE: A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral Rinse for Oral Chronic Graft Versus-Host Disease

Continuing Review Approved by the IRB on 08/22/16
Amendment Approved by the IRB on 02/14/17 (H) Date posted to web: 03/01/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Description of Research Study

You are being invited to participate in a research study testing whether a drug called clobetasol is effective in oral chronic graft versus host disease (oral cGVHD) - a common complication of stem cell transplantation that occurs in up to 60% of transplant patients. GVHD occurs when, after a transplant, the donor's cells attack and damage the recipient's tissues.

Clobetasol is a corticosteroid, a class of drugs that are commonly used to treat inflammation. Corticosteroids are known to affect the cells of immune system and may help to "turn down" the activity of the donor cells. Corticosteroids taken by mouth or injected have been proven to be effective for the treatment of cGVHD however they are associated with many side effects such as high blood pressure and diabetes. Topically applied (used on the surface, like creams or rinses) corticosteroids have relatively few side–effects but their role in the treatment of oral GVHD has not been well studied. Therefore, this study will investigate whether clobetasol rinse can decrease the severity of oral cGVHD in patients after their transplant and its effects on the cells of the lining of the mouth.

You can participate in this study if you:

- have signs of oral GVHD,
- are not allergic to clobetasol,
- are 12 years of age and older,
- did not have any changes in systemic (taken by mouth or injected, i.e. pills or shots) immunosuppressive therapy in the two preceding weeks
- are able to rinse with the study medication by mouth,
- are able to come back to NIH for follow-up appointments, and
- are not pregnant and are using a birth control method that meets the requirements of this study

What Are the Treatments and What is the Course of the Study?

Investigational Treatment

If you decide to participate, you will be first randomly (like the flip of a coin) assigned to receive either (1) clobetasol rinse or (2) placebo (an oral rinse that looks and tastes like the clobetasol rinse but has not active medication). You and the research team will not have a choice of which medication you receive in the first 2 weeks of the study. Likewise, neither you nor the investigators will know which medications you are taking until completion of the first 2 weeks of the study. However, in case of emergency, the information regarding which drug you are using will be available from the NIH pharmacy.

After the first 2 weeks, you will start using clobetasol rinse for another 2 or 4 weeks depending on whether you were originally assigned to placebo or clobetasol. That way every patient on the study will receive clobetasol for a total of 4 weeks.

You will rinse your mouth out with the study oral rinse 3 times a day after meals every day. You will take 10 ml of the oral rinse using the measuring cup, put it in your mouth and swish it around for 2 minutes and spit out the oral rinse into the sink. DO NOT SWALLOW THE RINSE! The oral rinse that we are using is not intended for internal use and we want to limit the

action of the drug to the mouth and decrease the effects of the steroid on the rest of the body. Please do not eat or drink for 30 minutes after use.

Should you swallow the rinse, please contact Dr. Pavletic.

Additional Treatment Period

After you have completed four weeks of clobetasol treatment, it may be possible for you to be treated with the clobetasol for up to an additional four weeks. You would need to restart the clobetasol within 90 days of your last dose of clobetasol in order for this to occur, and a follow-up exam at NIH must be done for you to qualify for re-treatment.

Non-Investigational Treatments

You will be given a painkiller rinse (viscous lidocaine, numbing rinse) that you can use to relieve the discomfort in the mouth. You can apply it to the affected areas in the mouth up to 3 times a day before eating but at least 30 minutes apart from the study rinse.

A potential anticipated side-effect of local corticosteroid treatment is yeast infection in the mouth. To prevent this, you will be asked to rinse once per day with an anti-fungal medication, nystatin suspension.

You will continue to take all medications that are prescribed as part of your post transplant care. However, no changes in the immunosuppressive medications will be allowed for the first two weeks of the study. The immunosuppressive medications include but are not limited to cyclosporine, tacrolimus (Prograf), mycophenolate (MMF, Cellcept) and prednisone. Changes in immunosuppressive medications will be allowed after the first 2 weeks of the study if necessary to control GVHD in sites other than the mouth. We will ask you about the use systemic steroids, immunosuppressants and pain medication use at the time of each evaluation.

Study Evaluations

Evaluations done to assess study eligibility

To ensure your safety, you will undergo a series of brief assessments to determine if you are a good candidate for protocol participation. These tests and procedures will be done under a separate screening protocol and will be fully described in that consent document.

History, oral exam, physical: We will perform a brief oral examination and explain the protocol procedures. We may also perform a physical exam and take your medical history.

Medication review: Some medications might reduce the effectiveness or increase the side effects of clobetasol and clobetasol may increase the side effects of or lessen the effectiveness of some medications. Therefore, we will need to review over-the counter-medications, health food supplements, and prescription medication that you are taking before you take part in this study.

Pregnancy testing: Women of childbearing age will have a pregnancy test, which must be negative before they take part in the study.

Evaluations and procedures done after consent but before starting study medication

Oral Exam: We will do a complete soft tissue exam of your mouth.

Oral photographs: We will take photographs of your mouth and the surrounding area.

Biopsy of Your Mouth: At the first visit, we will take one small piece of tissue (about 4mm across) from the inside of your cheek. We will numb the inside of your cheek and use a punch (size of a pencil eraser tip) to remove the tissue. This is a minor procedure with few side effects usually limited to some post-operative discomfort for about a day. Half of the tissue will be saved for research, and the other will be sent to the lab to be reviewed by a pathologist. Part of this tissue will be used for pathological examination to confirm your condition. Another part will be used in our lab to study factors that are associated with the development of GVHD in the mouth. This biopsy is required as part of this research study. After the initial biopsy, if you decide not to have further biopsies, you will still receive study drugs and have other tests as part of this study. You will be asked to sign a separate consent form for each biopsy procedure. Children will only have oral biopsy done if it is needed for medical reasons.

Saliva Tests: Saliva will be collected by spitting in the tube for 5 minutes. This will be done two times at each appointment: once while chewing a small piece of paraffin wax and once without wax. This is a simple procedure that does not have any risks or discomforts. We will use saliva samples to measure your salivary gland function and to study in our laboratory factors that may be associated with the development of GVHD including the types of protein in the mouth.

Blood sample collection: We will draw blood from your arm by a trained person. We will ask you sit or lie down when we take your blood. We will tie a large rubber band around the upper arm, and then we will cleanse the area on your arm with an alcohol swab, where we intend to take the blood. At the site we cleansed, we will place a tiny needle under the skin into a vein in your arm and we will fill-up 5 of tubes or less the size of your pinky with your blood. Once we are done getting the blood, we will remove the tiny need and cover the site with a band aid.

Questionnaires: You will be asked to fill out questionnaires which will measure your quality of life, your mouth pain and mouth dryness.

ACTH Stimulation Test: This test is used to evaluate the how well your adrenal glands work. Adrenal glands are normally responsible for production of steroids in the body. Sometimes, if steroids are taken for a long time, the adrenal glands react by decreasing their own production. This is called "adrenal suppression" and may result in decreased blood pressure and decreased ability to fight infection and cope with stress of trauma or surgery. Although, this generally happens when corticosteroids are given orally it is possible that in some cases corticosteroid from a rinse is taken by the body through oral lining. It is unknown how much effect this could have on the adrenal glands; therefore, we would like to evaluate your adrenal gland function by performing ACTH stimulation test.

This test is performed in the morning at 8 o'clock. You will have to be in a bed and we will give you an intravenous injection of a drug called "ACTH" or "cosynthropin" which is version of a

hormone normally produced by your pituitary gland. We will draw blood before and at 30 and 60 minutes after the injection to measure your cortisol levels. Children will only have an ACTH stimulation test done if it is needed for medical reasons.

Evaluations and procedures done during study drug administration (Day 0 to 4-6 weeks)

We ask that you return to the Clinical Center 2 weeks after starting study drug at which time baseline assessments will be repeated.

Oral exam: at each visit

Oral photographs: at each visit

Oral biopsy: at the 4-6 weeks visit (at the end of the treatment phase of the study). We will obtain an additional small (4 mm) punch biopsy sample for research purposes only. The biopsy will be taken from inside of your cheek from an area of the cheek near the healed spot from the first biopsy. This will be used to compare to the sample obtained before treatment was started. The biopsy to be performed is exclusively for research purposes and will not benefit you. It may help other people in the future.

Saliva samples: at each visit

Review of medications: at each visit

Study drug compliance: at each visit we ask that you return the medication diary and any unused medication so we can measure how much study drug you have taken.

Blood collection: at each visit

Questionnaires: You will be asked to assess your level of dry mouth and oral pain at each visit and complete one quality of life assessment at the 1-month visit only.

ACTH Stimulation Test: at the end of the investigational treatment or if you are taken off-study. This may be repeated at your final study visit, 8 weeks after starting active clobetasol rinse, if your doctors are concerned about adrenal suppression.

Follow-Up Evaluations

We will contact you every 3 months after you stop using clobetasol oral rinse for 6 months to assess duration of treatment response, recurrence of oral GVHD, and resolution of any side-effects you may have experienced. You will be contacted by a study team member by telephone or in person if you are already at the NIH for other treatment at a follow-up time point.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Related to Clobetasol:

Corticosteroids can be taken either internally as a pill or injections or topically as a cream or ointment. In this study the corticosteroid is used topically which hopefully will avoid many of the unwanted side-effects that are associated with the drug which include:

Likely

- Yeast infection (thrush). Short-term topical corticosteroid treatment is associated with few potential complications. The most common is yeast overgrowth. This is easily treated and does not require discontinuation of the study. To prevent this, you will be asked to rinse once per day with an anti-fungal medication, nystatin suspension. However, should oral yeast infection occur, you will be given a full course of medication that works in yeast infections. This will not prevent you from continuing in the study.

Less Likely

- Adrenal suppression: Problems associated with the adrenal gland are very rare (<1%) with topically applied steroids. Cases of adrenal suppression from topically-applied steroid creams have been reported in young children and adults. In some cases, the cream was applied too frequently, and the thinner skin of children was felt to enhance systemic absorption. In other reports, it was difficult to determine if there was true adrenal suppression. In this study adrenal function will be assessed at the beginning and the end of the study. Given the relatively short duration of this study, we do not expect side effects.
- Viral Reactivation: Local immunosuppression in the mouth from topical corticosteroid use may allow certain viruses present in your body, including herpes simplex virus, to reactivate in the mouth or elsewhere in your body. Symptoms of oral viral reactivation include oral ulcers and oral pain, similar to symptoms of oral cGVHD. You will be monitored for viral activity during the study. If reactivation is detected, you will be treated systemically with anti-viral medication.

Rare but Serious

- allergic reaction
- thinning of the lining of the mouth
- dilation of the small blood vessels in the mouth (spider veins).
- Very rare side effects possible with an individual with extensive internal absorption include acne-like skin rash, cataracts, bruising, water retention, heartburn or stomach upset, swelling of the parotid (large salivary glands) stomach ulcer, glaucoma, increased

body hair, high blood pressure, decreased blood potassium, hypopigmentation or other changes in skin pigmentation, and unusual loss of hair. These are side effects usually seen with systemic steroids, and are not expected with the topical steroid treatment used in this study.

Unknown side effects: You might also develop a side effect that hasn't yet been reported. Please tell us about any changes in your health that develop during and after your participation in this study. Treatment will be interrupted, delayed, or stopped if you develop any serious side effect. All complications from this treatment will receive full and prompt medical attention from NIH Clinical Center staff. You will be told of any newly reported risks that may affect your decision to continue in the study.

Because evaluation the safety of the oral rinse is one of the endpoints of this study you will be asked to evaluate your symptoms and any side-effects at follow-up visits. You will be asked to keep a medication diary to record when you take the study medication and any additional medications or side effects you experience while on this study. The study nurse or investigator will meet with you every month to review your progress and the medication diary.

Related to Oral Biopsy:

Oral biopsy is a minor surgical procedure that is performed under local anesthesia.

Likely

- Expect a minor degree of soreness. This generally goes away in a couple of days.

Rare but Serious

- Bruising and infection at the biopsy site. These are generally rare (<5%).

Related to blood testing: Collection of blood will be done primarily in association with post-transplant sampling.

Likely

- Some discomfort: You will feel a little needle pinch at the site the needle is inserted.
- Pain and bruising in the area where the blood was drawn.
- Lightheadedness, or on a rare occasion fainting

Related to Saliva collection: There is no associated risk or discomfort.

Related to ACTH Stimulation Test: Side effects of a single ACTH injection are rare, but may include changes in heart rate, increased blood pressure, dizziness, and pain at the injection site.

Risks regarding pregnant or nursing women: It is not known whether clobetasol can harm pregnant women or nursing babies. Pregnant women or women who are breast-feeding may not take part in this study. Women who are participating in this study must be using effective

methods of birth control during their enrollment in this study. Effective methods include abstinence, surgical sterilization, barrier methods (such as diaphragm, condom, cervical cap, and sponge), birth control pills, and Depo-Provera.

Potential Benefits of Participation

The aim of this study is to see if this experimental clobetasol mouth rinse will be beneficial in treatment of oral GVHD. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include healing of oral ulcers or lessening of your symptoms, such as pain, that are caused by the oral GVHD. There may be indirect benefits associated with thorough oral examinations performed in the study. Because there is not much information about clobetasol's effect in this form on oral cGVHD we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have chronic GVHD.

Alternative Approaches or Treatments

We do not know whether the treatment used in the study will have any effect (good or bad) on your disease. If your disease worsens after two weeks of treatment with clobetasol you will be taken off study and offered alternative treatment.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for your oral cGVHD without being in a study. Alternative treatment for oral GVHD includes other topical or systemic steroids and systemic immunosuppressive drugs.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain and other problems caused by oral cGVHD. It does not treat oral cGVHD directly.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if we determine that your oral condition worsened at the 2 week of receiving clobetasol rinse
- if a change in systemic immunosuppression is necessary to control GVHD outside the mouth in the first 2 weeks of the study
- if you have side effects from the treatment that your doctor thinks are too severe

- if study if you are unable to follow the study procedures and evaluations.
- if new information shows that another treatment would be better for you
- if the study doctor decides to end the study

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Spectrum Chemicals or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Optional Blood Tests

We would like measure the rate at which the study drug reaches the bloodstream after one two-minute rinse in a subset of patients. This would involve a single appointment at which you would rinse with the study drug for 2 minutes, and then a small blood sample would be taken at 0 minutes, 15-45 minutes, and 90-120 minutes after rinsing. This would be done at the same visit as one of your scheduled study visits. We do not expect that much of the study drug will reach the bloodstream, however it will provide valuable information to know how quickly this occurs. This information will help us screen patients in this study for side effects, and will improve the design of future treatments.

You will be given the chance to decide if you want to participate at the time of the procedure. No matter what you decide to do, it will not affect your care or study participation.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.
We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic, M.D., Building 10, Room 3-3330 Telephone: 240-760-6174. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM AUGUST 22, 2016 THROUGH AUGUST 21, 2017.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____