A Controlled Study of the Efficacy of Botulinum Toxin A (Botox) for the Treatment of Social Anxiety Disorder (SAD)

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CONTACT INFORMATION

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CLINICAL STUDY PROTOCOL SUMMARY

Sponsor: Dermatology and Cosmetic Surgery Associates, LLC

Investigational Treatment: Five injections of Botox will be administered at a single treatment visit.

Title of Study: A Controlled Study of the Efficacy Botox Treatment for the Treatment of Social Anxiety Disorder (SAD)

Date: 3/8/2016

Number of centers: One

Primary Objective: The objective of this proposed study is to obtain data on the efficacy of Botox in reducing symptoms of social anxiety disorder (SAD) in male and female patients between the ages of 18 and 65 years old. Efficacy will be determined by using a continuous measure of outcome, the Liebowitz Social Anxiety Scale (Primary outcome) (LSAS; Fresco et al, 2001) and dichotomous indicators of response (Primary outcome) (LSAS <50) and remission (Secondary Outcome) (LSAS <30). Subjects will be assessed using: the self-rated LSAS and the self-rated version of the BDI-I at screening, 4 weeks, and 8 weeks.

Statistical Considerations: An ANOVA with repeated measures to determine whether there are statistical differences between the interventions will be used. Because the effect size of the intervention is unknown, the power statistics required to obtain significant differences between placebo and Botox cannot be calculated.

Number of Patients Planned: Up to 100 subjects will be screened in order to enroll 30.

Diagnosis and Criteria for Inclusion: Patients will be included in this study if they meet all of the following criteria:

Written informed consent is obtained;
They are a 18 to 65 years old;

A primary diagnosis for SAD as diagnosed by the MINI, and their current episode must be at least one month in length; A total score on the LSAS of 60 or greater
Women of childbearing potential (WOCBP) are on an acceptable form of birth control and are not pregnant or lactating;
They are judged by the investigator to have the capacity to understand the nature of the study;
They are willing to comply with all the requirements of the study.
They are considered by the investigator to be likely to adhere to the protocol.

Criteria for Exclusion: Patients will be excluded from this study if they meet any of the following criteria:

They have ever been treated with botulinum toxin A ;
They have another Axis I disorder as a principal diagnosis in the 6 months prior to screening;
They have a history of substance abuse or dependency in the 2 months prior to screening;
Pregnant women, lactating women, and women of childbearing potential not using medically accepted forms of contraception;
Patients with current or recent suicidality;
Scoring 10 or greater on the BDI
Scoring 2 or greater on the suicide question of the BDI
Psychotic disorders, bipolar disorder;
They are considered to be at a significant risk of committing homicide;
They have an unstable medical condition;
Women of childbearing potential (WOCBP) who are pregnant or are considering becoming pregnant during the length of the study;
They are regarded, for any reason by the principal investigator as being an unsuitable candidate for the protocol.
There has been a change in their medication or psychotherapy treatment regimen in the month preceding screening;

Mode of Administration: Patients will be randomly assigned to the active group or control group in a 1:1 ratio. Patients in the control group will be injected with a saline solution. Patients in the active group will receive 40 units of Botox (females) or 50 units (males). For females, 8 units will be injected into the procerus and 8 units into both the right and left medial and lateral corrugators. For males, 10 units will be injected into each location.

Method of Blinding: This will be a double-blind study. The clinician administering the injections will be blinded. After the initial visit, to help maintain the blind, all data will be collected via a web portal with online questionnaire assessments.

Duration of Treatment: The study will be divided into three phases: screening and enrollment, treatment, and follow-up. Patients who meet all criteria will be randomized at the screening visit. The follow –up phase will last eight (8) weeks after the investigational product is administered. Patients will be instructed to complete the LSAS and BDI online at week 4 and 8.

General Design and Methodology: Prior to screening, potential participants will fill out the LSAS and BDI online in order to determine initial eligibility. Those who meet the criteria will be

scheduled for an in-person screening visit. At screening, patients will sign consent and be diagnosed by means of the MINI (Sheehan et al,1998) , and will have a DSM-IV diagnosis of Social anxiety disorder (SAD). They will complete the LSAS. They will also complete the patient-rated BDI (Beck et al.,1961). Patients who meet all criteria will be randomly assigned to receive either the investigational product or placebo. Patients will be photographed, at the initial visit, at rest. The study medication or placebo will be injected within 7 days of clinical assessments into the procerus and corrugator supercilii frown muscles of each patient by a physician's assistant who is experienced in the administration of this medication. Four weeks ± 7 days, and eight weeks ± 7 days following the injection, each patient will complete online assessments. Patients will complete online the adverse events (AEs) and concomitant medications questionnaires will be at week 4 and 8.

Investigational New Drug (IND) Application: This study is exempt from the requirement for an IND submission based on the following criteria: Botox is lawfully marketed in the United States. There is no intent to report the findings of this trial to the FDA in support of a new indication or any significant change in the labeling of the drug. This study is not intended to support a significant change in the advertising of the prescribed drug. Compared to the current labeling of Botox, there will be no change in the route of administration, the dosage level, or any other factor that significantly increases the risk, or decreases the acceptability of the risk, associated with the use of the drug. Botox is approved for doses up to 400 units. We will use 40 or 50 units. The patient population will be different compared to the current labeling, which specifies bladder dysfunction, chronic migraine, upper limb spasticity, cervical dystonia, blepharospasm, strabismus and primary axillary hyperhidrosis. The change in population will not significantly increase the risk. All participants in the study will be medically stable adults.

BACKGROUND INFORMATION

Introduction

Investigational Treatment

The use of botulinum toxin A to correct glabellar frown lines is an effective and popular cosmetic procedure with more than 1 million treatments per year in the United States alone (Carruthers, A.). Botulinum toxin type A marketed commercially as BOTOX® Cosmetic (Botox), is produced from fermentation of Hall strain Clostridium botulinum type A grown in a medium containing casein hydrolysate, glucose, and yeast extract, intended for intramuscular use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying. Each vial of Botox contains 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

Botox blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of

acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, Botox produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by Botox.

Botox is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

Botox is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

Findings from Non-clinical and Clinical Studies

Glabellar Lines

Two phase 3 randomized, multi-center, double-blind, placebo-controlled studies of identical design were conducted to evaluate Botox for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The studies enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Subjects were injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units. In these studies, the severity of glabellar lines was reduced for up to 120 days in the Botox group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown, and by subject's global assessment of change in appearance of glabellar lines. Analysis of the limited number of patients 65 years or older suggested a lower treatment-associated response compared to patients less than 65 years of age. (Botox website)

Depression

The first open label trial of Botox to the glabellar muscle complex to treat unipolar depression was published in 2006. Since that time, three randomized double blind placebo-controlled trials were conducted to assess the efficacy of Botox treatment of the glabellar muscle complex in major depression. All three studies showed a response rate of 50 to 60%, and the remission rate of approximately one-third. To date, no clinical trials of Botox have been conducted in SAD.

Social Anxiety Disorder (SAD)

Social anxiety disorder (SAD) is a common psychiatric condition marked by persistent fear and anxiety of one or more social or performance situations. The lifetime prevalence of the disorder is 12%, and leads to significant morbidity for those affected. The only FDA approved treatments for SAD have response rates of 40 to 60 %, and remission rates of 20%. Therefore, there is a real need for the development of new and effective treatments for SAD.

Patients suffering from SAD either avoid situational triggers or endure intense anxiety and distress, leading to an impaired social life in either scenario. SAD is characterized by an overactive anxiety pathway with a perceptual and cognitive bias towards threat.

The amygdala, a limbic region with multiple projections to cortical and subcortical regions, is thought to be critically involved in the regulation of emotion, with a general role in directing attention to affectively salient stimuli, recruiting and coordinating cortical arousal for optimizing sensory and perceptual processing of ambiguous or novel stimuli.. A tight link between fear and the amygdala has been suggested. Fear related neuronal circuits involving the amygdala are thought to play a role in the generation of social withdrawal, fear, and anxiety.

Recently, two studies have linked botulinum toxin A treatment of the frown with down-regulation of amygdala activity. Hennenlotter et al, using fMRI imaging, reported that patients who received botulinum toxin A injections into their frown muscles had decreased activity in the amygdala and its coupling with brain stem activity when mimicking angry facial expressions. Further research has confirmed that amygdala activity in response to angry faces was decreased when the frown muscles were paralyzed by botulinum toxin A injection. Furthermore, amygdala activity returned to its original state after the effects of the botulinum toxin A injection had worn off, confirming that botulinum toxin A reversibly severed afferent feedback from the corrugator muscle to the amygdala.

Given that SAD patients show abnormal patterns of amygdalar activation after viewing emotional faces, we believe that there is a good likelihood that some of the symptoms of SAD will improve after botulinum toxin A treatment of the frown.

Known and Potential Risks and Benefits to Human Subjects

Post-marketing safety data from Botox and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases of higher doses, be observed beyond the site of local injection. The symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects.

However, adverse effects are dependent upon the site of injection. No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of Botox for glabellar lines have been reported. Similarly, no definitive serious adverse event reports of distant spread of toxin effect associated with Botox for blepharospasm at the recommended dose or for strabismus at the labeled doses have been reported.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been

reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Pre-Existing Neuromuscular Disorders

Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of Botox.

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PURPOSE OF THE STUDY AND STUDY OBJECTIVES

Purpose of the Study

The purpose of the study is to evaluate the efficacy of botulinum toxin A as a treatment for SAD.

Study Objectives

The primary objective of this proposed study is to obtain data on the efficacy of Botox in reducing symptoms of SAD in male and female patients between the ages of 18 and 65 years old.

Efficacy will be determined by using a continuous measure of outcome, the Self Rated Liebowitz Social Anxiety Scale (Fresco et al, 2001) and dichotomous indicators of response (LSAS < 50) and remission (LSAS < 30).

Patients will also be assessed with the self-rated version of the BDI at screening, 4 weeks, and 8 weeks.

STUDY DESIGN

The study will begin in May 15, 2016 and be completed by September 2017. Approximately 30 patients will be randomized and enrollment will be complete when that number is reached. It is estimated that up to 100 patients will have to be screened in order to randomize 30.

Potential participants will begin by going to REDCap, a mature, secure web application for building and managing online surveys and databases, and providing basic demographic information (age, sex, and employment status). They will then complete the LSAS and BDI on REDCap. If they meet the inclusion criteria, they will be asked for their name, telephone number, and email address, and a screening visit will be scheduled for an in-person screening appointment. If they do not, they will be provided with a list of referrals where they can obtain

clinical treatment. No identifiable information will be collected from these people. Their anonymous data will be used to compare the characteristics of those who met the criteria for participation, and those who did not. This information is routinely requested by journal editors in order to help readers evaluate the generalizability of the results.

At screening, patients will be asked to give consent, and the MINI diagnostic interview will be administered by a study coordinator with extensive experience administering the MINI and other psychiatric scales. The diagnosis will be confirmed by a clinical interview with the principal investigator, a board certified psychiatrist. He will also collected information on concomitant medications, and review the inclusion exclusion criteria with the potential participant. The PI will also evaluate the stability of the patient, comorbid medical and psychiatric conditions, and safety considerations such as the presence of suicidal ideas. WOCBP will be asked to take a urine pregnancy test.

People who decline to consent, or don't meet the inclusion/exclusion criteria, will be provided with a list of referrals where they can obtain clinical treatment. If the person is in crisis, the crisis will be managed by the PI. If they will not be in the study, all of their identifying information will be destroyed. The anonymous data will be kept as described above. If they don't come to the screening visit, an attempt will be made to reschedule it. If it is not successfully rescheduled, the identifying information will be destroyed. Participants who meet all criteria will be photographed, and randomly assigned to receive either the investigational product or placebo (saline).

All procedures except photography and administration of investigational product will take place in the clinical offices of GWU MFA. For photography and administration of the investigational product, patients will be transported by taxi or private car service to the Chevy Chase Cosmetic Center, located at 8401 Connecticut Avenue, Suite 210, Chevy Chase, MD 20815. After the study procedures are complete, participants will be transported back to GWU MFA or to a nearby Metro station, if they prefer.

The injectable syringes will be prepared by Dr. Finzi at the Chevy Chase Cosmetic Center. Syringes will contain either Botox or saline based on the randomization scheme. They will be marked with numbers written on tape affixed to clear envelopes that contain only the individual syringes. After being made, syringes will be stored in a refrigerator at 4 degrees Celsius in the Chevy Chase office. All patients will be examined and injected by a physician assistant, Allison Wagner, who has been trained in the practice of injection, and was the injector for the Finzi and Rosenthal clinical trial studying Botox for the treatment of major depressive disorder. Dr. Finzi will shall have no contact with patients, to maintain the blind.

The study medication or placebo will be injected into the procerus and corrugator supercilii frown muscles of each patient by a physician or physician's assistant.

Four and eight weeks following the injection, patients will contacted and asked to complete the online LSAS and BDI self- assessments as well as reporting on concomitant medications and adverse events.

Participants will receive a gift card for up to $45 at the completion of the study. They will receive $25 if they complete the screening visit, and additional $10 if they complete the first post-treatment online assessment, and another $10 if they complete the second post-treatment online assessment.

Safety Measures

Adverse events will be collect via online assessments, and will be reviewed by the investigator within 24 hours. Patients will be contacted by telephone, or asked to come in for a face-to-face meeting if the investigator believes that the patient is at risk or if further evaluation of the adverse event is needed. Patients will be instructed to contact the investigator by telephone at any time if they have concerns about adverse events they may be experiencing.

All adverse events that occur during the study period, that is, from the signing of the informed consent through the follow-up period, will be documented regardless of the severity of the event or judged relationship to the study treatment. The clinical course of each adverse event will be monitored until resolved or stabilized, until the patient is referred to the care of a local health care professional, or until determination of a cause unrelated to the study technique or study procedure is made.

The investigator will capture onset and resolution dates, duration, action taken, treatment administered and outcome for each adverse event. The relationship of the adverse event to study treatment and procedures and the severity and seriousness will also be recorded.

Serious Adverse Events

Adverse events are classified as either serious or non-serious. A serious adverse event is any adverse event that results in any of the following outcomes or actions:
Death
A life-threatening adverse event (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
Inpatient hospitalization or prolongation of existing hospitalization
A persistent or significant disability/incapacity
A congenital anomaly/birth defect
An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Hospitalizations scheduled for an elective procedure or for treatment of a preexisting condition that has not worsened during participation in the study will not be considered serious adverse events.

Other Safety Measures and Variables: Concomitant Therapy or Medication

Co-administration of Botox and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Stopping Rules and Discontinuation Criteria

A participant may discontinue participation in the study at any time for any reason (e.g., lack of efficacy, consent withdrawn, or adverse event). The investigator may discontinue a patient from the study at any time for any reason (e.g. non-adherence to the protocol, emergence of psychiatric instability).

Confidentiality and Privacy Regarding Participants

The investigator will assure the privacy of all patients, including their personal identity and all personal medical information at all times. Data will be stored on the secure REDCap system or on a password-protected computer in a locked office. Hard copies of data will be stored in a locked office, and destroyed after the data is entered into a computer. Participants will be assigned a code number, and all data will be identified by this code. The code key will be kept separate from the data, and will be destroyed five years after publication of the study results. Photographs of the participants will be altered to eliminate the possibility of identification five years after publication of the study results. This will entail cropping out the entire face except for the area that was injected. The retained image will not include the participants' eyes, or any features below the eyes. The remaining, fully anonymized data will be kept indefinitely. Privacy will be assured by conducting all in-person procedures in private clinical offices or exam rooms.

Conflict of Interest

Eric Finzi, MD, PhD, a sub-investigator on the study, holds a patent on the use of Botox for social anxiety disorder. The conflict of interest will be managed in the following way: Dr. Finzi will prepare the investigational product according to the randomization scheme. He will have no contact with participants. He will not collect or analyze data. The principal investigator, who has no conflict of interest, will approve all manuscripts prior to submission and publication.

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APPENDIX

Beck Depression Inventory – attached
Liebowitz Social Anxiety Scale - attached