A Phase II Trial and Comparative Study on the Efficacy and Safety of Botox (Onabotulinumtoxin A) Injection Therapy for Carpal Tunnel Syndrome

The following protocol describes a phase II trial that consists of both a safety and activity (SA) trial and a comparative study of the experimental drug Onabotulinumtoxin A against a current clinical standard therapeutic treatment, Methylprednisolone, a corticosteroid.

1. PROTOCOL SYNOPSIS

Title: A Phase II Trial and Comparative Study on the Efficacy and Safety of Botox (Onabotulinumtoxin A) Injection Therapy for Carpal Tunnel Syndrome
Study Phase: 2
Indication: Carpal Tunnel Syndrome symptom management

Primary Objective: To evaluate the effect of Onabotulinumtoxin A on clinical symptoms

1. **Safety**: To evaluate the safety, tolerance, and identify adverse outcomes/effects of the treatment.

2. **Efficacy**: A $\geq$30% improvement in strength for the Dynamometer and Jamar Pinch gauge. A $\geq$ 20% reduction in median nerve cross-sectional area at wrist. A $\geq$ 15% reduction in Distal Motor and/or Sensory Latency

Secondary Objective: Comparative study to evaluate the efficacy of Onabotulinumtoxin A on clinical symptoms and patient quality of life compared to standard medical treatment of corticosteroid injection Methylprednisolone.
Hypothesis: In subjects with Carpal Tunnel Syndrome, Onabotulinumtoxin A is as effective at treating clinical symptoms and improving patient quality of life as Methylprednisolone.
Primary Endpoint: Change from baseline in:

1. Levine Symptom and Function Severity Scales

2. Median Nerve Compression as measured by cross-sectional area and distal latencies in neuromuscular ultrasound and oscilloscope readings

3. Dynamometer and Jamar Pinch gauge

Secondary Endpoint: Statistically comparable results in primary endpoint measurements between Onabotulinumtoxin A and Methylprednisolone.
Study Design: Phase 2, multi-center, randomized and voluntary, triple-blind, parallel group study of subjects with idiopathic Carpal Tunnel Syndrome. Of the 85 subjects, 25 will be placed in the SA trial. The remaining 60 participants were voluntarily recruited to the comparative study. A 40 unit dose injection of Onabotulinumtoxin A will be administered to 55 subjects. A 1mL suspension of 40mg of Methylprednisolone (Depo-medrol) will be injected into 30 subjects.

Sample Size: Approximately 85
Summary of Subject Eligibility Criteria: Adults 18 to 60 years of age with confirmed medical diagnosis of idiopathic Carpal Tunnel Syndrome for $\geq$ 12 months with active symptoms for at least 3 months and poor response to wrist splinting. For the complete list of eligibility criteria, refer to the section Subject Eligibility.

2. BACKGROUND AND RATIONALE

A. Carpal Tunnel Syndrome

The carpal tunnel is an osteofibrous canal in the wrist that serves as an enclosure space for the throughput of the median nerve [10]. Microtraumas to or compression of the median nerve via the carpal tunnel lead to nerve pain and swelling of the canal structure. Deposition of fluid within the tunnel can also occur as a result of agitation to this area. These insults to the body, if repetitive, can lead to a long-term increase in carpal tunnel pressure causing compression of the median nerve. This compression marks the onset of Carpal Tunnel Syndrome (CTS). CTS can either be classified as idiopathic or non-idiopathic. An idiopathic disease is one that arises from an unknown origin. Non-idiopathic conditions may be due to physical trauma or as part of a natural progression of a disease. This study will focus on idiopathic CTS.

B. The Current Treatment: Methylprednisolone

A common treatment for CTS is injectable corticosteroids near the carpal tunnel [4]. One of the clinical benefits to steroidal use is their effectiveness in reducing inflammation. By reducing inflammation near the carpal tunnel, the compression on the median nerve can be reduced and CTS symptoms temporarily alleviated. However, steroids in the Methylprednisolone family can have negative side effects such as: weight gain, worsening diabetic conditions, high blood pressure, and potassium loss (potentially dangerous for heart health) [9]. Thus, **finding an alternative treatment for individuals with CTS and additional health conditions, where steroid use is a health risk, is a matter of interest.**

C. The Experimental Treatment: Onabotulinumtoxin A

The cosmetic effects of Botox have been well documented, but new clinical benefits to the neurotoxic protein are currently under research. The toxin produced by the bacterium Clostridium botulinum has been shown to relieve headaches, chronic pain, and various types of neuropathic pain due to its ability to block nerve signalling for muscle contraction when injected locally [11]. For the current study, Botox will be injected into the muscles surrounding the carpal tunnel to alleviate the tendon tension that causes tunnel pressure to increase [10]. An inherent risk in Botox injection lies in the accuracy of the injection such that no other muscle group or nerve complex is unintentionally paralyzed, therefore only experienced medical professionals may administer the drug.

3. OBJECTIVES

A. Primary

To evaluate the effect of Onabotulinumtoxin A on clinical symptoms

1. **Safety**:
   To evaluate the safety, tolerance, and identify adverse outcomes/effects of the treatment.

2. **Efficacy**:
   To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$ 30% improvement in the Jamar Pinch gauge tests.

   To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$ 20% reduction in median nerve cross-sectional areain a neuromuscular ultrasound.

   To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$ 15% reduction in Distal Motor and/or Sensory Latency

B. Secondary

Comparative study to evaluate the efficacy of Onabotulinumtoxin A on clinical symptoms as compared to the standard medical treatment, Methylprednisolone.

C. Exploratory

1. To evaluate the effect of Onabotulinumtoxin A from baseline as measured by Levine Symptom Severity Scale (SSS) severity scores.

2. To evaluate the effect of Onabotulinumtoxin A from baseline as measured by Levine Function Severity Scale (FSS) severity scores.

3. To evaluate the effect of Onabotulinumtoxin A compared to Methylprednisolone as measured by Levine Symptom Severity Scale (SSS) severity scores.

4. To evaluate the effect of Onabotulinumtoxin A compared to Methylprednisolone as measured by Levine Function Severity Scale (FSS) severity scores.

4. EXPERIMENTAL PLAN

A. Study Design

For a general outline, this is a phase 2, multi-center, randomized and voluntary, triple-blind, parallel group study of subjects with idiopathic Carpal Tunnel Syndrome. The study begins with an initial screening phase (1-3 weeks) where patient baseline information is obtained via Levine severity scale surveys, pinch test, nerve conduction studies, and neuromuscular ultrasound. During this time the patients are also re-evaluated to ensure they fit the eligibility criteria. Baseline is established over 2 weeks, and then a single dose treatment phase (1 day) will occur. Following treatment administration, a 12 week patient follow-up phase consisting of 4 meetings to assess clinical outcomes and safety will take place. A final phone interview will occur 4 weeks after the last in-person follow-up to assess patient satisfaction since treatment.

The study will be conducted in two parts. An initial SA trial and if no early stoppage occurs, the study will continue with the comparative study.

Subjects will be accepted to the study on a voluntary basis for either Botox or Methylprednisolone treatment. See Subject Enrollment for more information on randomization and recruitment. Of the 85 subjects, 25 will be placed in the initial SA trial.

B. Number of Sites

At least 15 Neurology centers and clinics across Michigan will participate in the study. Additional sites may be added.

C. Number of Subjects

Approximately 85 subjects have been recruited to be enrolled in the study. Twenty-five patients will be assigned to the SA trial for Onabotulinumtoxin A. Thirty additional patients will be assigned to the Onabotulinumtoxin A group and 30 to the Methylprednisolone group for the comparative study.

D. Estimated Study Duration

The intended length of the study for a participating subject is up to 23 weeks. This time frame includes the initial screening through the final follow-up via phone interview with a couple of weeks added for buffer. Figure S1 demonstrates an example study calendar schedule for a subject. This amount of time is necessary to not only study the short-term effects of Onabotulinumtoxin A, but its long-term effects also. Methylprednisolone is a long-term therapeutic option for individuals with CTS, with relief from symptoms lasting as long as six months.

5. SUBJECT ELIGIBILITY

A screening log will be kept with limited information about each potential subject prior to enrollment. During enrollment, each subject must sign an informed consent form regarding their intention to be treated before any assessment, allocation of treatment, or study specific procedure can occur.

A. Inclusion Criteria

- Adults between the ages of 18 and 60 at start of enrollment
- Confirmed idiopathic Carpal Tunnel Syndrome diagnosis by a medical doctor at ≤ 50 years of age
- On-staff doctor confirms idiopathic CTS during initial screening

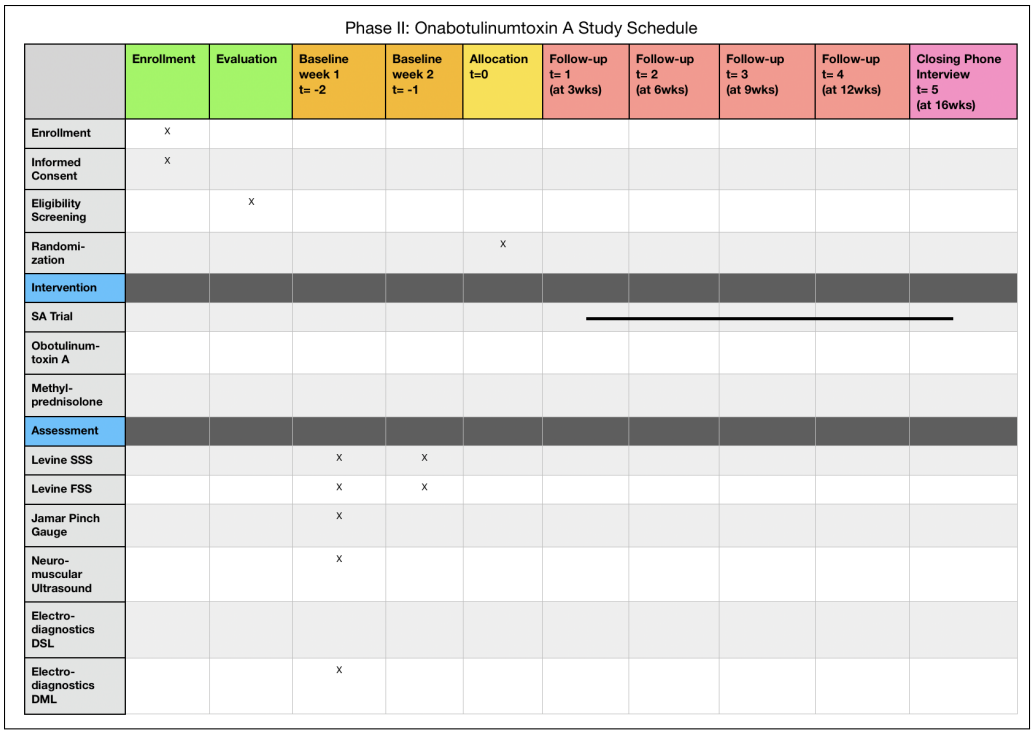

Figure S1. Sample Study Calendar for Individual Subject

- CTS symptom duration for at least 3 months with poor response to wrist splinting

Criteria to be assessed during Baseline Phase and prior to Randomization

- Median nerve cross-sectional area (CSA) $\geq 11mm^2$ as indicative by neuro-muscular ultrasound
- Median Nerve Distal Sensory Latency (DSL) $\geq$ 2.2 ms measured by electrodiagnostic oscilloscope [3]
- Median Nerve Distal Motor Latency (DML) $\geq$ 3.5 ms measure by electrodiagnostic oscilloscope

B. Exclusion Criteria

- Patients with prior carpal tunnel surgery
- Previous steroid or Botox injection to treat CTS or otherwise
- Allergies to any of the active or inactive ingredients in Onabotulinumtoxin A or Methylprednisolone
- Prior diagnosis of a Neuromuscular Junction disorder [11]
- Currently pregnant or breastfeeding
- Prior diagnosis of any form of diabetes mellitus
- Known abuse of drugs and/or alcohol [2]
- Severe medical illness

6. SUBJECT ENROLLMENT

Subjects were recruited on an informed, voluntary basis through participating physicians in neurology and affiliated centers across Michigan. Subjects, prior to enrollment, had provided consent to either Onabotulinumtoxin A treatment, Methylprednisolone treatment, or both. Patients solely preferring Methylprednisolone were referred to a separate study and excluded from the current.

Before subjects may be enrolled, all subjects must personally: sign and date the informed consent form (ICF), sign and date an Institutional Review Board/Independent Ethics Committee (IRB/IEC) protocol form. A subject is considered enrolled at randomization. The baseline screening phase begins once the ICF is signed and ends when the subject is randomized or fails to meet all the inclusion and none of the exclusion criteria [8].

A. Randomization

Of the 85 subjects who indicated no preference, i.e providing consent to either treatment, 60 were randomized into the comparative study for receiving either Onabotulinumtoxin A or Methylprednisolone. The remaining 25 subjects will go to the initial SA trial to study the efficacy of Onabotulinumtoxin A.

Randomization will be carried out by block randomization method into parallel groups for the comparative study to balance allocation size and reduce variability. Ten of the twenty possible permutation blocks of size 6 will be randomly selected with replacement.

Subjects, Investigators, and Outcome Assessors will be blinded to the allocation of treatment for all subjects. Treatment administrators will not be blinded due to the risks associated with injecting Onabotulinumtoxin A. Treatment administrators will be trained on administering the drugs and answering subject questions and concerns in a non-differential manner.

A.1. Site Personnel Access to Individual Treatment Allocations

A subject's treatment allocation will be unblinded only in the case of serious or adverse events at the risk of the subjects health or as a necessity for further management of the subject [8]. In any other event, unblinding of allocation will be considered a deviation from protocol.

7. TREATMENT PROCEDURE

Treatment allocation occurs over the course of one day, following randomization and baseline screening approval. All treatments will be packaged without any identifiable indication of treatment to individuals other than the treatment administrator. Dosage will be fixed for the duration of the study and for all subjects. All patients will be monitored on-site for 1 hour post-allocation for any adverse events with a phone-interview follow-up the day after.

For patients allocated to the current standard of treatment, the treatment administrator will inject a 1mL suspension of 40mg of Methylprednisolone into the carpal tunnel of the wrist. For patients allocated to the experimental treatment (including SA trial subjects), the treatment administrator will inject 40 units of Onabotulinumtoxin A, divided equally between two injection sites: the opponens pollicis and abductor pollicis brevis muscles in the hand [11].

A. Implementation of Early Stopping in Study

The initial SA trial will be used to determine any early stoppage of the study with regards to the effectiveness of Onabotulinumtoxin A. Simon's Two-Stage Minimax design will be used to determine the efficacy of Onabotulinumtoxin A on CTS [1]. The null hypothesis that the true response rate is 0.10 will be tested against a one-sided alternative. In the first stage, 15 subjects will be accrued. If there are 1 or fewer responses, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 25. The probability of early stoppage is 0.5490. Please refer to Figure S2 for additional details.

A.1. Adverse Events

Due to the allocation procedure being a single-dose, one day event, the subjects will be monitored according to the treatment procedure. Should any event arise related to study-specific procedures, subjects will receive immediate care from either staff on-site or study-compensated care at their nearest healthcare facility.

If there is early stopping of the study, subjects will be referred to other recruiting trials for corticosteroid or botox injection. Subject contact information, if consented to, will be retained for future reference should the study be reopened.

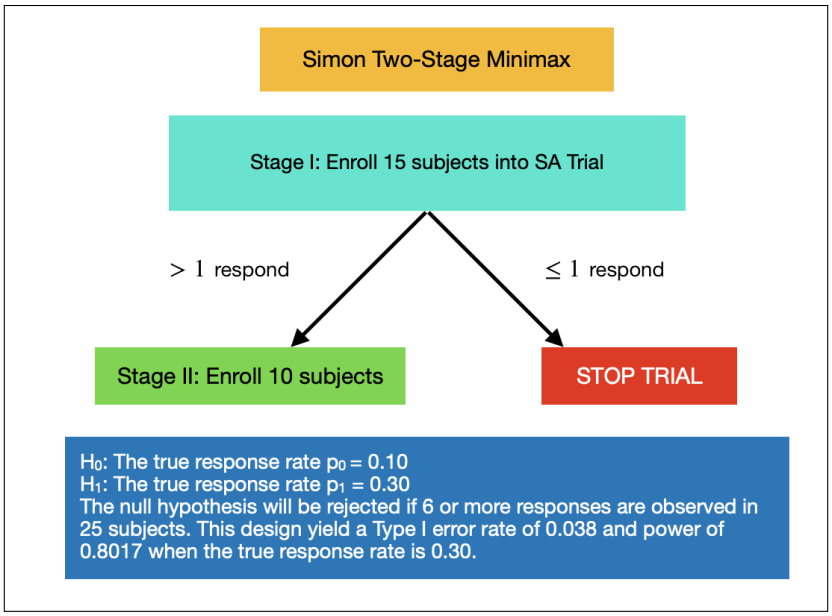

Figure S2. Simon Two-Stage Minimax Design

8. STUDY PROCEDURES

The study will begin with the SA trial to determine the safety, activity, and efficacy of Onabotulinumtoxin A on CTS. If no early stoppage is necessary, the study will begin the secondary objective by initiating a comparative study between the experimental drug and the current standard of treatment for CTS, Methylprednisolone.

A. Informed Consent

All subjects must sign and date an informed consent form (ICF) approved jointly by the drug sponsoring company, the IRB, and the IEC before any study-specific procedures occur.

B. Physical Examination

All subjects must receive written approval from their primary care physician and the on-staff study physician before any study-specific procedures can occur. A comprehensive physical exam will be carried out by the on-staff study physician. Additionally, all subjects must meet all of the inclusion criteria and none of the exclusion criteria.

C. Study-specific Procedures and Screenings

For the three following assessments, data will be recorded 6 separate times during the baseline phase. At the end of baseline phase, averages for each subject will be recorded and used as a baseline comparison to the observations obtained during follow-up. Post-allocation and at each follow-up the same tests will be done during each visit according to the indicated description.

C.1. Neuromuscular Ultrasound

An ultrasound of the median nerve will be carried out once at the beginning of each assessment. The median nerve cross-sectional area will be measured. A normative range is around $9 - 12mm^2$ with non-normative values being larger for patients with CTS [7]. This will also be used as a measurement of compression of the median nerve.

C.2. Electrodiagnostics

Electrophysiological measurements will be taken for the distal sensory and motor latency of the median nerve. Latency is conduction speed (ms) measured as the interval between nerve stimulation of a muscle and the observed response. Observed latencies are longer in individuals with CTS than healthy individuals.

C.3. Dynamometer and Jamar Pinch Gauge

Grip of the dynamometer will be assessed via 3 maximum strength grip attempts at 45 minute intervals. The readings on the dynamometer will be recorded and averaged. The Dynamometer will also be used to measure short-term endurance grips. Three maximum grip strength attempts will be tested over 30 second intervals to examine any percentage decrease in strength with repeated use [5].

The Jamar Pinch Gauge will be used to measure pinch strength for three pinch types: 3-fingered, lateral and pulp pinches. 3 maximum strength attempts over 45 minute intervals will be recorded and averaged.

D. Clinical Outcomes Assessment Surveys

Four weeks after the end of the follow-up phase of the comparative study, a subject satisfaction survey will be given over phone to assess the patient's quality of life since the treatment.

D.1. Levine Survey

The Levine Symptom and Function Severity Scale questionnaires are based on a multiple-choice question and answer format, in which each answer has a score value [6]. The "severity" rating is based on the average score value from the questionnaire. This will be used as another measure of subject quality of life in response to the treatment that is based on their own subjective experience.

This survey will be administered during the same week of follow-up, prior to on-site meeting via email.

9. STATISTICAL CONSIDERATIONS

A number of hypotheses for the difference in means between experimental and standard treatment will be tested for each of the assessments. Additionally, dependent samples hypothesis testing will be carried out for the average difference in assessment values for pre- and post-treatment in the SA trial. A general list of the statistical methods to be used to analyze the data gathered from the observations in the SA trial and comparative study includes:

- Descriptive Statistics
- Mean calculations (for all assessments)
- Standard Deviation calculations (for all assessments)
- Dependent Samples t-test (for SA trial pre- versus post-treatment response)
- Two-Sample t-test (for the comparative study between Onabotulinumtoxin A and Methylprednisolone)

SAS statistical software will be used to analyze the data.

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