VASCULITIS CLINICAL RESEARCH CONSORTIUM

TAPIR

THE ASSESSMENT OF PREDNISONE IN REMISSION TRIAL

The Assessment of Prednisone In Remission Trial (TAPIR) – Patient Centric Approach

Vasculitis Clinical Research Consortium (VCRC)

Protocol Number 5526B
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1. Protocol Synopsis Table

Protocol Number:	5526B
Protocol Title:	**T**he **A**ssessment of **P**rednisone **I**n **R**emission Trial (TAPIR) – Patient Centric Approach
Study Chairs:	Jeffrey P. Krischer, Ph.D. Peter A. Merkel, M.D., M.P.H.
Statistician:	David Cuthbertson, M.S.
Participating Sites:	University of Pennsylvania University of South Florida
Activation Date:	February 17, 2014
Sample Size:	A maximum of 79 randomized participants for a total sample size of 159 evaluable randomized participants between the Centers of Excellence (CoE) and Patient Centric (PC) study arms.
Target Enrollment Period:	5 years
Study Design:	Randomized controlled trial to evaluate the effects of using low-dose glucocorticoids as compared to stopping glucocorticoid treatment entirely. Participants will be randomized 1:1 to: • taper their prednisone dose down to 5 mg/day using a tapering schedule determined by their treating physician and stay at 5 mg/day of glucocorticoids for the duration of the study (approximately 6 months), or • taper their prednisone dose down to 0 mg/day using a tapering schedule determined by their treating physician and stay at 0 mg/day for the duration of the study (approximately 6 months). Target enrollment is randomization of a maximum of 79 eligible patients. Participant data collected via this study will be combined with that from a complementary study conducted at VCRC clinical centers (N=159 evaluable participants between the two study arms).
Primary Study Objective:	Physician decision to increase prednisone for disease relapse
Primary Outcome Measure:	The proportion of participants who increase prednisone for disease relapse within 6 months of randomization
Secondary Study Objective:	• Rates of flare sub-types: severe vs. non-severe within 6 months of randomization • Time to event (flare) • Health-related quality of life • Safety outcomes

- Serious adverse events
- Infections

- Protocol performance
  - Patient characteristics
  - Protocol compliance
  - Participant retention
  - Data completeness
  - Timeliness of data entry
  - Data accuracy

Secondary Outcome Measures

1. Flare type (severe or non-severe)
2. Duration of remission
3. Patient-reported outcomes (PROMIS measures)
4. Frequency of adverse events

Eligibility/ Exclusion Criteria:

Inclusion Criteria

1. Established diagnosis of granulomatosis with polyangiitis (GPA) (verified by medical record review by Protocol Oversight Management team) where patients will need to meet at least 2 of the 5 modified ACR criteria, at least one of which must be d or e:
   a. Nasal or oral inflammation, defined as the development of painful or painless oral ulcers or purulent or bloody nasal discharge
   b. Abnormal chest radiograph, defined as the presence of nodules, fixed infiltrates, or cavities.
   c. Active urinary sediment, defined as microscopic hematuria (>5 red blood cells per high power field) or red blood cell casts)
   d. Granulomatosis inflammation on biopsy, defined as histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area. Note: Pauci-immune glomerulonephritis seen on kidney biopsy will suffice for this criterion.
   e. Positive anti-neutrophil cytoplasmic antibody (ANCA) test specific for proteinase-3 measures by enzyme-linked immunoassay

   Patients who are MPO positive or ANCA negative are still eligible for this study if they meet the criteria above and are felt to have GPA.
2. Active disease within the prior 12 months (initial presentation or relapse) that at time of active disease required treatment with prednisone ≥ 20 mg/day
3. Disease remission at time of enrollment
4. Prednisone dose at time of enrollment of ≥ 5 mg/day and ≤ 10 mg/day

5. Participant age of 18 years or greater
6. If the patient is taking an immunosuppressive medication agent other than prednisone (maintenance agent) then the maintenance agent must be at a stable dose for one month prior to enrollment with no plans by the treating physician to change the dose (other than for safety purposes/toxicity) for the duration of the study (through the month 6 visit or early termination). Acceptable maintenance agents include azathioprine, leflunomide, 6-mercaptopurine, methotrexate, mycophenolate mofetil, mycophenolate sodium, or rituximab. Patients may be on trimethoprim/sulfamethoxazole (TMP/SMX) for use as either a maintenance agent or for prophylaxis for infection. TMP/SMX may be used in combination with other drugs.
   6.1 If the patient is regularly taking trimethoprim/sulfamethoxazole at any dose then the patient is eligible if there no plans by the treating physician to change the dose after enrollment (other than dose reduction or discontinuation for safety purposes/toxicity) for the duration of the study
7. Agreement from Treating Physician that randomized treatment assignment is standard of care
8. Participant's Treating Physician is located in the United States

Exclusion Criteria

1. Comorbid condition that has moderate likelihood of requiring a course of prednisone within one year of enrollment (e.g. COPD, asthma, adrenal insufficiency)

Statistical Considerations (analysis plan): Participant data collected via this study will be combined with that from a complementary study (N=159). The percent of participants whose physician decided to increase glucocorticoid dose for disease relapse will be compared between those randomized to receive 0 mg prednisone and 5 mg prednisone by a Z test with pooled variance. Descriptive statistics with appropriate 95% confidence intervals will be calculated for all secondary outcomes. Differences in maintenance regimens (i.e., immunosuppressive agents other than glucocorticoids, such as azathioprine, methotrexate, or rituximab) will be included as covariates in assessing the study end point.

Sponsors: National Heart Lung and Blood Institute (NHLBI)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

1a. Brief Summary

This study is a novel approach to conducting a randomized clinical trial in the community setting.

This study is funded through the National Institutes of Health with the purpose of exploring novel methods of conducting clinical trials. The study will be conducted by the Vasculitis Clinical Research Consortium (VCRC) and the Data Management and Coordinating Center (DMCC).

1b. Detailed Description

Patients with granulomatosis with polyangiitis (GPA) will be recruited via the Rare Disease Clinical Research Network (RDCRN) VCRC Contact Registry, social media, and the study public website. The VCRC contact registry consists of over 3,000 subjects with vasculitis, of which over 1,600 have reported a diagnosis of GPA. Several social media sites including Facebook and Twitter will have an information page about the study.

The RDCRN VCRC Contact Registry and the social media sites will direct patients to the study public website. The study public website will be developed and maintained by the Data Management and Coordinating Center at USF. The website will provide information about the study including inclusion/exclusion criteria, whom to contact with questions, requirements for participation in the study, and the study design of tapering to 0 mg/day of prednisone or 5 mg/day of prednisone. The public website will also contain the interactive informed consent form to enroll in this study.

Potential participants will be presented with a video about the study that explains the goals of the research and the risks and benefits of the study. Participants will be able to access this video continually during the consenting process and after enrollment. The participant will be able to contact study staff through multiple channels including phone, email and social media.

At time of enrollment, participants will need to be taking prednisone at a dose ≥ 5 mg/day and ≤ 10 mg/day. Once the participant has enrolled in the study, the participant will have access to a study website that is personalized for each participant. Participants can keep track of their progress in the study, access the online consent form, and access study forms. Participants will receive their treatment randomization assignment via the Participant website as well as a Physician packet that the participant will take to his/her treating physician explaining the research study and the participant's involvement in the study. The Physician will have the option to consent to be contacted to answer questions about the research study.

In order for the participant to be eligible for the study, the treating physician needs to agree that a prednisone dose of 5 mg/day or 0 mg/day is standard of care. The Protocol Oversight Management Team will review the patient's medical records to determine if the participant meets the eligibility requirements. Participants will taper his/her prednisone under the guidance of his/her treating physician. Once the participant reaches a prednisone dose of 5 mg/day, the participant will be randomized to continue prednisone at 5 mg/day or taper prednisone to 0 mg/day. The Participant's treating physician will be notified of the participant's randomized dose. Participants will be followed for 6 months from randomization. Throughout the study, participants will have the option to consent to be contacted via phone to answer additional study questions. At the conclusion of the study participants will be thanked for their participation.

2. Study Endpoints

2a. Primary Outcome

The **primary study endpoint** will be the physician decision to increase prednisone for disease relapse.

2b. Secondary Outcomes

The secondary study endpoints include:

- Rates of flare sub-types: severe vs. non-severe within 6 months of randomization
- Time to event (flare)
- Health-related quality of life
- Safety outcomes
  - Serious adverse events
  - Infections
- Patient characteristics
- Protocol Performance
  - Protocol compliance
  - Subject retention
  - Data completeness
  - Timeliness of data entry
  - Data accuracy

3. Background and Rationale

3a. Background

The Rare Diseases Clinical Research Network (RDCRN) (www.RareDiseasesNetwork.org) is a highly successful and innovative international clinical trials network of 17 distinct clinical research consortia led by

the Office of Rare Diseases Research with collaboration from NCI, NINDS, NIAID, NIAMS, NICHD, NIDCR, NIDDK, and NHLBI, and central coordination provided by the Data Management and Coordinating Center at the University of South Florida.

The Data Management and Coordinating Center (DMCC) houses all RDCRN data and coordinates all protocol activity for the Vasculitis Clinical Research Consortium centrally via in-house scalable and customizable electronic data capture systems. The DMCC will design and implement all facets of data collection and develop and manage the web tools (Facebook presence, etc.) for recruitment and consenting.

The Vasculitis Clinical Research Consortium (VCRC)
(www.RareDiseasesNetwork.org/vasculitis) is a founding member of the RDCRN and the major clinical research infrastructure in North America for the study of vasculitis. The research conducted by the VCRC includes clinical trials, outcome measures development, large cohort and clinical epidemiologic studies, specimen collection and repository, translational investigations including biomarker discovery and genomics, and research training. The VCRC includes 11 major vasculitis clinical centers in the US and Canada and dozens more partner sites in the US, Europe, Asia, and Australia. Each US VCRC site coordinates its research activities with a CTSA program. The VCRC has substantial funding from the NIAMS, FDA, NINDS, and various private foundations and industry partners. The VCRC investigators include nearly every major researcher involved in vasculitis in the US and Canada. Several of the VCRC investigators will make up the Protocol Oversight Management Team.

The RDCRN VCRC Contact Registry
The RDCRN VCRC Contact Registry is an online mechanism for patients to register themselves or a member/members of their family who have been diagnosed with Vasculitis. The Contact Registry provides ongoing email contact to each registrant, providing information when studies are activated. The RDCRN VCRC Contact Registry has over 1,600 participants with GPA enrolled.

Granulomatosis with polyangiitis (Wegener's) (GPA) is a primary systemic vasculitis, predominantly involving microscopic blood vessels with no or scanty immune deposits. GPA is strongly associated with circulating auto-antibodies to neutrophils (ANCA) and is one of a group of conditions known as ANCA-associated vasculitis (AAV) (1). The cause of AAV is unknown. AAV has an annual incidence of 20 per million and an approximate prevalence of 200/million (2). It is a multi-system autoimmune disease that causes tissue damage especially to the respiratory tract and kidneys, and causes early mortality, organ failure including end stage renal disease, and chronic morbidity (3).

Prior to the availability of effective treatment, AAV was almost universally fatal, with a 93% mortality within 2 years due to pulmonary and renal failure (4). The

introduction of what is now termed conventional immunosuppressive treatment transformed survival (5). Administration of cytotoxic immunosuppression (cyclophosphamide, rituximab, methotrexate) and glucocorticoids (GC) for at least one year induces remission in approximately 80% of patients. GC are a standard of care in the treatment of AAV. High doses of GC early in disease although undeniably reduce disease activity due to their anti-inflammatory and immunosuppressive properties also increase the risk of infection particularly in the elderly and in the presence of uremia. There is a major unmet need for safer therapy that leads to sustained treatment free remission in patients with relapsing disease, which will reduce drug toxicity that results from cumulative exposure to immunosuppression and glucocorticoids.

Clinical Manifestations

Classic GPA involves the upper respiratory tract, the lungs, and the kidneys. Distinctive features may also occur in the eyes, ears, and other organs. Approximately 90% of patients with GPA have nasal involvement, including crusting, bleeding, and obstruction, erosive sinus disease and subglottic stenosis (6). Two principal forms of ear disease, conductive and sensorineural hearing loss, are typical of GPA. Orbital masses ("pseudotumors") and scleritis are the signature ocular lesions of GPA. The clinical manifestations of GPA in the lung range from asymptomatic nodules to fulminant alveolar hemorrhage. The most common radiographic findings are pulmonary infiltrates and nodules. Renal involvement is the most ominous clinical manifestation of GPA. The clinical presentation of renal disease in GPA is that of rapidly progressive glomerulonephritis with: hematuria, red blood cell casts, and proteinuria. Without appropriate therapy, end-stage renal disease may ensue within days to weeks. Sixty percent of patients with GPA have musculoskeletal symptoms during their disease courses. Arthralgias/arthritis are frequently the presenting complaint of GPA. Skin lesions in GPA include the full panoply of lesions associated with cutaneous vasculitis such as purpura, nodules, and other lesions. Neurologic manifestaions of GPA include mild-severe sensory and motor peripheral neuropathy (especially mononeuritis multiplex), cranial neuroapthies, and rarely, central nervous system disease.

3b. Rationale

Treatment of GPA includes the combination of high-dose glucocorticoids (GC) and an immunosuppressive agent, including cyclophosphamide, rituximab, methotrexate, azathioprine, or other drugs. Remission is usually achieved within a short time (1-2 months) and glucocorticoid taping is begun within one month of initiation. A major unanswered question is what tapering regimen to use for GC and whether patients with GPA are better off being maintained on low-dose prednisone or attempting to come off of glucocorticoids altogether. Patients successfully treated for GPA continue, however, to have high rates of relapse associated with the accrual of organ damage and exposure to toxic medications. Optimal treatment strategies for patients with GPA remain to be defined. Studies

in the last 20 years have addressed the use of immunosuppressive medications in GPA (7, 8). Unlike immunosuppressive medications, the use of GC has not been rigorously evaluated. There is little evidence to guide the use of GC and there is considerable practice pattern variation, especially after the induction of remission. Of particular debate is whether low-dose GC contributes to maintaining the remission of GPA. Some experts support the use of long-term, low-dose GC, claiming improved disease control, a subsequent reduction in the exposure to toxic immunosuppressive medications, fewer periods of exposure to high-dose GC, and a reduction in the accumulation of disease-related scarring. Others argue that the use of long-term, low-dose GC is ineffective at reducing relapses and exposes patients to the potential toxicity of high cumulative doses of GC. The efficacy of long-term, low-dose GC for the treatment of AAV to prevent relapses or reduce treatment-related toxicity is a matter of continued debate, even within the Vasculitis Clinical Research Consortium, and is of great interest to patients. This issue is considered quite important for its clinical implications as well as its potential impact on design of randomized clinical trials in GPA since both the "taper to 0 mg/day" and "maintain at 5 mg/day" prednisone schedules have been used in the major randomized clinical trials in this field.

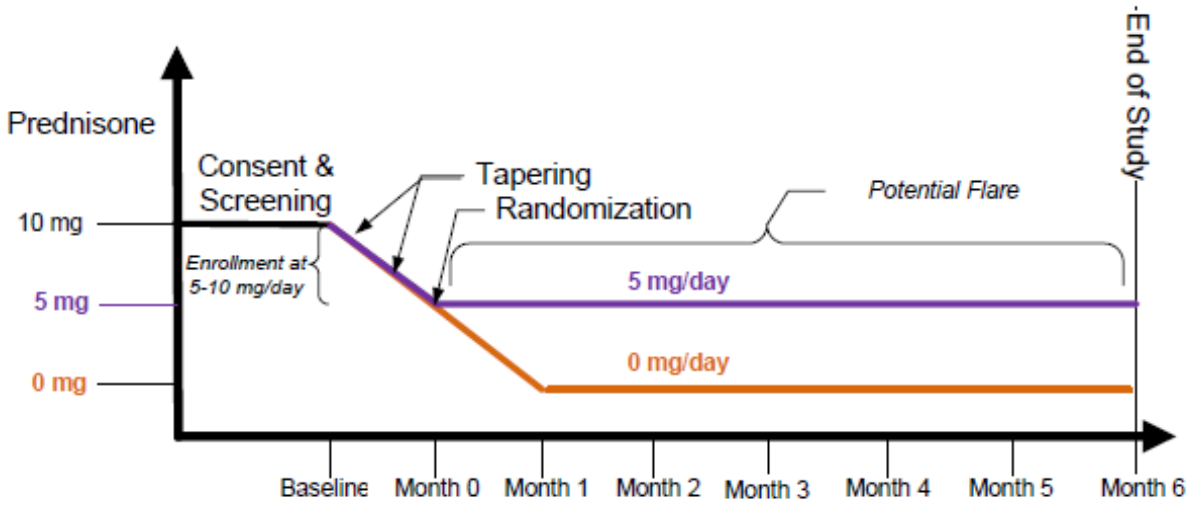
4. Study Design and Methods

4a. Overview

This open label pilot study will randomize a maximum of 79 participants (for an evaluable total sample size of 159 participants between this study and a complementary VCRC study) with GPA in remission affecting the sinonasal tract, oral mucosa, skin, musculoskeletal system, pulmonary parenchyma, or other disease features that warranted an administration of 20 mg/day within the last 12 months. At the time of enrollment, participants will need to be taking prednisone at a dose of $\geq$ 5 mg/day and $\leq$ 10 mg/day. All enrolled participants will be instructed to reduce the daily dose of prednisone according to their treating physician. Once participants reach a prednisone dose of 5 mg/day, they will be randomized at a 1:1 ratio to continue prednisone at 5 mg/day or to taper prednisone to 0 mg/day. Participants will be followed for approximately six months from reaching a prednisone dose of 5 mg/day.

It is recognized that patients who receive repeated doses of rituximab will usually receive an intravenous dose of glucocorticoids on the days they receive an infusion of rituximab as part of usual care; these additional doses of glucocorticoids will be allowed for under this protocol and receipt will not be considered criteria for achieving a relapse/primary endpoint. The doses of glucocorticoids given on days of administration of rituximab will be recorded.

4b. Study Diagram



4c. Recruitment

Potential research participants will be recruited online through the RDCRN VCRC Contact Registry, social media outlets and a study public website. Social media pages will be created on Facebook, Google+, Twitter and other social media outlets to advertise for this study. The RDCRN VCRC Contact Registry and social media outlets will direct patients to the study public website.

Vasculitis patient advocacy groups will promote this randomized clinical trial at in-person meetings and in newsletters.

An additional avenue to identify and recruit participants will be for the TAPIR trial to partner with two separate Clinical Data Research Networks (CDRNs), part of the Patient-Centered Outcomes Research Network (PCORnet). Each CDRN has access to the electronic health records (EHR) of > 1 million patients. A validated computable phenotype for granulomatosis with polyangiitis will be run through the CDRN health system databases to identify patients that are potentially eligible for this trial. These patients will be sent correspondence referring them to the main TAPIR website to consent and enroll in the trial. Since the CDRNs have access to these patient's electronic health records, this partnership would also make EHR data available on drug dosing and outcomes for individuals who consent and join the study. These CDRN networks will obtain separate IRB approval for their identification and referring activities. This new approach is consistent with patient-centric approach to this study and the goal of exploring novel methods to conducting clinical trials.

All recruitment material will be reviewed by the appropriate oversight bodies (Institutional Review Boards (IRBs), Research Ethics Boards (REBs), Data and Safety Monitoring Board (DSMB), etc.).

Prior to protocol version 04Apr17, participants receiving rituximab for induction of remission were not eligible to participate in this study while patients receiving rituximab for maintenance of remission were allowed to participate if the last dose of rituximab for maintenance of remission was administered at least one month prior to enrollment and no additional doses were planned for future administration. With the approval of the amended protocol dated 04Apr17, participants receiving rituximab at the time of screening will be allowed to participate in the study regardless of any planned future additional administrations of rituximab. The dose of rituximab and glucocorticoids given with the rituximab infusion will be prescribed by the local physician. The study team will collect information about the dose of rituximab and the dose of glucocorticoids given with each infusion of rituximab for data analysis purposes.

4d. Eligibility Criteria

4di. Inclusion Criteria

1. Established diagnosis of granulomatosis with polyangiitis (GPA) (verified by medical record review by the Protocol Oversight Management Team) where patients will need to meet at least 2 of the 5 for the classification of GPA, at least one of which must be criterion d or e.

   The modified ACR criteria are:

   a. Nasal or oral inflammation, defined as the development of painful or painless oral ulcers or purulent or bloody nasal discharge
   b. Abnormal chest radiograph, defined as the presence of nodules, fixed infiltrates, or cavities.
   c. Active urinary sediment, defined as microscopic hematuria (>5 red blood cells per high power field) or red blood cell casts
   d. Granulomatosis inflammation on biopsy, defined as histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area. Note: Pauci-immune glomerulonephritis seen on kidney biopsy will suffice for this criterion.
   e. Positive anti-neutrophil cytoplasmic antibody (ANCA) test specific for proteinase-3 measures by enzyme-linked immunoassay

   Patients who are MPO positive or ANCA negative are still eligible for this study if they meet the criteria above and are felt to have GPA.
2. Active disease within the prior 12 months (initial presentation or relapse) that at time of active disease required treatment with prednisone ≥ 20 mg/day (verified by medical record review by the Protocol Oversight Management Team)
3. Disease remission at time of enrollment (verified by medical record review by the Protocol Oversight Management Team)
4. Prednisone dose at time of enrollment of ≥ 5 mg/day and ≤ 10 mg/day
5. Participant age of 18 years or greater

6. If the patient is taking an immunosuppressive medication agent other than prednisone (maintenance agent) then the maintenance agent must be at a stable dose for one month prior to enrollment with no plans by the treating physician to change the dose (other than for safety purposes/toxicity) for the duration of the study (through the month 6 visit or early termination). Acceptable maintenance agents include azathioprine, leflunomide, 6-mercaptopurine, methotrexate, mycophenolate mofetil, mycophenolate sodium, or rituximab. Patients may be on trimethoprim/sulfamethoxazole (TMP/SMX) for use as either a maintenance agent or for prophylaxis for infection. TMP/SMX may be used in combination with other drugs.
   6.1 If the patient is regularly taking trimethoprim/sulfamethoxazole at any dose then the patient is eligible if there no plans by the treating physician to change the dose after enrollment (other than for dose reduction or discontinuation for safety purposes/toxicity) for the duration of the study.
7. Agreement from Treating Physician that 0 mg/day of prednisone or 5 mg/day of prednisone is standard of care
8. Participant's Treating Physician is located in the United States

4dii. Exclusion Criteria

1. Comorbid condition that has moderate likelihood of requiring a course of prednisone within one year of enrollment (e.g. COPD, asthma, adrenal insufficiency)

4e. Randomization Procedures

At randomization, all participants will be on prednisone dose of 5 mg/day. All participants with GPA confirmed by the Protocol Oversight Management Team will be randomized to continue their prednisone at 5 mg/day or to taper their prednisone to 0 mg/day. If necessary, the treating physician will have 5 weeks to taper patients from 5 mg/day to 0 mg/day.

4f. Visit Frequency/Visit Schedule

This study will occur primarily online.

Participants will enroll online. After enrollment, participants will have access to a personalized participant website. Participants can keep track of their progress in the study and access the online consent form and study materials including a packet that the participant will send to his/her treating physician. The packet explains the research study and notifies the treating physician of the participant's interest in participating in the study. The treating physician will confirm (or not confirm) that the participant is eligible for the study and confirm (or not confirm) that 5 mg/day or 0 mg/day of prednisone is standard of care for that patient. The participant may provide the study packet to their treating physician in person or

may send the packet to their treating physician to complete via mail/fax/etc. An in-person visit with the participant's treating physician is not required for any study related reasons (participant may still need to visit physician for clinical care.)

Participants will reach the end of the study participation when the participant has completed the duration of the study.

Participants will be informed that they are free to withdraw from the study at any time without compromising the relationship with their physician or their future medical care.

4g. Data Elements for Collection

Participants will be asked to send or to authorize their treating physician to send the DMCC medical history data including physical examination data, blood results, chest radiographs and other diagnostic images. This information is collected as part of routine clinical practice and is not mandated by the protocol. The information will be used to confirm eligibility by the Protocol Oversight Management Team.

Data Collection Points	**Time Period**		
Completed by Participants	**Start of Study**	**During Study**	**End of Study Participation**
Informed Consent	X		
Demographics	X		
Disease Information	X	X	
Disease Activity, Medication history (including rituximab usage) and/or Adverse Symptoms	X	X	X
Quality of Life questionnaires	X	X	X
Prednisone Dose	X	X	X
Qualitative Measures*	X	X	X
Completed by Protocol Oversight Management Team			
GPA Diagnosis Verification	X		
AE and/or Flare Verification†			X
Completed by Treating Physician±			
Qualitative Measures±			X

**Participants may consent to be contacted to answer additional study related questions*
†AE and/or Flare Verification may not be required for all participants
±Treating Physicians may consent to be contacted to answer study questions

4h. Retention Strategies

Retention will be encouraged by frequent electronic contact with the participant. Contact can be made to the participant via email, social media outlets, text messaging, mobile phone applications, etc. These messages can be study specific and remind the participant to report disease activity, prednisone dose, etc., disease specific including information about GPA, prednisone use, etc. and other items that patients with GPA are often interested about such as rare diseases.

5. Safety Monitoring and Adverse Event Reporting

5a. Nature of Study

Participant enrollment may only begin with IRB approved consent forms.

This study meets the federal definition of low risk.

5b. Adverse Events

Participants will be encouraged to report disease activity and adverse symptoms throughout their participation on the study. The Protocol Oversight-Management Team will review reported disease activity and adverse symptoms. The participant will remain under the care of his/her treating physician during the study and will be instructed to consult his/her treating physician for any event requiring medical attention.

Only those events associated with the conduct of the study and as defined above are reportable. Adverse events believed to be related to other medications provided to the participants (such as rituximab) for the purpose of maintaining remission, are not considered reportable as they are not considered a study medication in this protocol.

Glucocorticoid Side Effects:
Glucocorticoids have been used therapeutically in humans since 1949 and their side effects are well recognized. The main toxicities of prednisone include infections, hyperglycemia, hypertension, cataracts, osteoporosis, avascular necrosis, gastrointestinal irritation, mood disturbances (including psychosis), bruising, skin changes including acne and striae, increase in appetite and weight, and redistribution of fat. Prednisone is not known to have teratogenic effects on the developing fetus and there has been no evidence to date of an effect on fertility. However, prednisone can cause problems during pregnancy for both the mother (risks of weight gain, gestational diabetes, and infection) and the developing fetus as a result of the maternal problems.

The risks as listed on the package insert for prednisone (Deltasone®) include (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=3735):

- Fluid and Electrolyte Disturbances
  - Sodium retention
  - Fluid retention
  - Congestive heart failure in susceptible patients
  - Potassium loss
  - Hypokalemic alkalosis
  - Hypertension
- Musculoskeletal
  - Muscle weakness
  - Steroid myopathy
  - Loss of muscle mass
  - Osteoporosis
  - Tendon rupture, particularly of the Achilles tendon
  - Vertebral compression fractures
  - Aseptic necrosis of femoral and humeral heads
  - Pathologic fracture of long bones
- Gastrointestinal
  - Peptic ulcer with possible perforation and hemorrhage
  - Pancreatitis
  - Abdominal distention
  - Ulcerative esophagitis
  - Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
- Dermatologic
  - Impaired wound healing
  - Thin fragile skin
  - Petechiae and ecchymoses
  - Facial erythema
  - Increased sweating
  - May suppress reactions to skin tests
- Metabolic
  - Negative nitrogen balance due to protein catabolism
- Neurological
  - Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment
  - Convulsions
  - Vertigo
  - Headache
- Endocrine
  - Menstrual irregularities
  - Development of Cushingoid state
  - Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
  - Suppression of growth in children

- Decreased carbohydrate tolerance
- Manifestations of latent diabetes mellitus
- Increased requirements for insulin or oral hypoglycemic agents in diabetics

- Ophthalmic
  - Posterior subcapsular cataracts
  - Increased intraocular pressure
  - Glaucoma
  - Exophthalmos
- Additional Reactions
  - Urticaria and other allergic, anaphylactic or hypersensitivity reactions

6. Data Analysis and Statistical Considerations

The primary objective of this study is to compare the physician decision to increase prednisone for disease relapse between those randomized to receive 0 mg/day of prednisone and those randomized to receive 5 mg/day. Disease relapse is defined to be an increase in BVAS score necessitating an increase in glucocorticoid dose. Should an enrolled and randomized study participant increase their dose for any other reason after randomization, with the exception of co-administration of glucocorticoids as part of re-treatment with rituximab, the participant will remain on study but not be included in the primary analysis. This, therefore, is a modified intent to treat design. Insofar as their effect on sample size, they would be treated as among the dropout group.

6a. Sample Size

A meta-analysis of 13 published RCTs was performed to examine the question of the clinical utility of low-dose prednisone in remission-maintenance of AAV (10). This study suggested that the expected relapse rate among those treated with continued low-dose of prednisone is 15% (95% CI:10-19%) before 12 months compared to 43% (95% CI:33-52%) among those in whom glucocorticoids was stopped completely (10). It is anticipated that 41% of the participants in the study overall will have received rituximab at the time of screening. This number is based on the prediction that 70% of the remaining subjects enrolled once the 04Apr17 protocol version is implemented will be on rituximab at Screening. Furthermore, it is estimated that the six month relapse rates for these participants will be 20% for those on 0 mg prednisone and 10% for those on 5 mg prednisone. Based on the combination of these populations, the expected relapse rate for those treated with low dose prednisone is 14% and 35% for those prednisone free. Based on these estimates, a target accrual of 142 patients randomized 1:1 to the two treatment arms would have 80% power (comparing 6 month flare rates of 13.2% to 32.9%), using a 2-tailed significance level of 0.05 and a Z test with pooled variance. Assuming a maximum 11% drop out rate due to subject choice or related to data quality concerns, we plan to enroll 159 evaluable participants into the trial from the two arms. (The original 20% drop out rate for the entire trial was adjusted to account for the fact that 59 participants have

completed the trial at the time of the implementation of the 04Apr17 protocol. Thus, the adjusted overall drop-out rate for the entire trial following the 04Apr17 protocol amendment is estimated to be a maximum of 11% allowing for the remaining enrollees to have a 20% drop out rate). A maximum of 79 of the 159 participants will be accrued through this protocol, with the remainder being obtained from a complementary study.

If the dropout rate exceeds 11% or the relapse rate on the 5 mg. falls below expectations such that the study power is compromised, then the target enrollment will be increased to maintain the desired detectable effect size.

6b. Stratification

The study will be stratified by whether the subject is newly diagnosed or previously experienced a disease flare requiring steroids according to the eligibility criteria. Differences in maintenance regimens (i.e., other non-glucocorticoid immunosuppressive agents such as azathioprine, methotrexate or rituximab) will be included as covariates in assessing the study end point. Stratification is intended for balancing only and the study is not powered for within-stratum comparisons.

Data on disease relapse will be reported by study participants utilizing the web tools provided by the DMCC.

6c. Secondary outcomes

Secondary outcomes including rates of flare sub-types (severe vs. non-severe), time to event (flare), adverse events associated with prednisone, health related quality of life measures (PROMIS), and safety outcomes will be estimated both overall and by treatment arm, and appropriate 95% confidence intervals will be calculated.

7. Data Management

All study data will be collected via systems created in collaboration with the DMCC and VCRC and will comply with all applicable guidelines regarding patient confidentiality and data integrity and security.

7a. Registration/Online Consent

Participants will register for the study online via the study public website. After consenting to the study, the participant will enter an email address and password. An email will be sent to the participant. The participant will not be enrolled in the study until after the participant returns to the public website via the link in the email.

7b. Data Entry

The participant will create a username and password to access the secure Participant website. The participant will directly enter demographics, disease and prednisone dose information directly online.

7c. Data Quality Control

Data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Internal validity checks for reasonableness and consistency will be built into the initial tables and cross tabulations.

8. Protection of Human Subjects

The proposed research project is a randomized clinical trial of 0 mg or 5 mg daily of prednisone in patients with GPA. Prednisone is the only therapeutic intervention of any type included in the research plan.

The risks of participating in this study are expected to be low and will be due to the use of prednisone. A potential risk is a risk of loss of privacy. Participants may find the study through social media outlets. If the participant utilizes their name in messages or in account names in social media, privacy may be lost. The investigators will not share personal information or identifiers with anyone outside of the research team. The demographic and disease information collected are not anticipated to be psychologically harmful or stressful.

If adverse effects from the study are incurred, the participant will be instructed to utilize full resources of the hospital or their treating physician. Throughout the informed consent form, when discussing the study with study staff, and in media messages, participants will be instructed to seek medical attention from his/her treating physician if an adverse event occurs.

There are no benefits to study participants for their involvement in this research. If the study leads to higher quality care or therapeutic trials for vasculitis then study patients could theoretically benefit in the future. All participants will potentially have the satisfaction of helping to contribute to medical knowledge of vasculitis. Further understanding of the clinical aspects of vasculitis is of great medical importance. Because progress in understanding this disease is expected from this study it is felt that the potential benefits of this research outweigh the risks of participation.

Knowledge to be gained from this study could be potentially highly important. Understanding the optimum use of low-dose glucocorticoids is important. This study could lead to better care and less toxic treatment regimens. Insight into the conduct of clinical trials in vasculitis could be gained and this might lead to more efficient clinical trials for patients with vasculitis.

9. References

1. Niles JL. Antineutrophil cytoplasmic antibodies in the classification of vasculitis. Annu Rev Med 1996;47:303-13.
2. Watts RA, Scott DG, Lane SE. Epidemiology of Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. Cleve Clin J Med 2002;69 Suppl 2:SII84-6.
3. Mohammad AJ, Bakoush O, Sturfelt G, Segelmark M. The extent and pattern of organ damage in small vessel vasculitis measured by the Vasculitis Damage Index (VDI). Scand J Rheumatol 2009;38(4):268-75.
4. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983;98(1):76-85.
5. Hoffman GS, Leavitt RY, Fleisher TA, Minor JR, Fauci AS. Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. Am J Med 1990;89(4):403-10.
6. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116(6):488-98
7. Mukhtyar C, Guillevi n L, Cid M, Dasgupta B, De Groot K, Gross W, Hellmich B, Jayne D, Kallenberg C, Merkel PA, Raspe H, Salvarani C, Scott DGI, Stegeman C, Hauser T, Watts R, Westman K, Witter J, Yazici H, Luqmani R. EULAR Recommendations for the management of large vessel vasculitis. Annals of Rheumatic Diseases. 2009; 68:103-106.
8. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. New England Journal of Medicine. 2010; 363:221-32.
9. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33(8):1101-7.
10. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. Arthritis Care Res (Hoboken). 2010. 8:1166-73.