PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL

MGH Vasculitis and Glomerulonephritis Program

Maintenance of ANCA vasculitis remission by intermittent rituximab dosing based on B cell reconstitution vs a serologic ANCA flare. (MAINTANCAVAS)

I. Background and Significance

Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis is a systemic autoimmune disease characterized by small vessel inflammation caused by pathogenic autoantibodies directed against proteinase 3 (PR3) or myeloperoxidase (MPO)(1). The disease is highly morbid, with greater than 80% of patients suffering serious complications from irreversible organ damage or treatment-related adverse events.(2)

The devastating complications of ANCA vasculitis warrant prompt and aggressive immunosuppression. Treatment is divided into two phases: induction immunosuppression to achieve remission, and maintenance immunosuppression to prevent relapse. Cyclophosphamide has traditionally been used as the backbone of induction regimens for ANCA Vasculitis. While effective, cyclophosphamide is associated with serious adverse events including infection, gonadal toxicity leading to infertility, bone marrow suppression, and malignancy(2-4). These complications have spurred the search for novel treatments with more favorable toxicity profiles. Recently, the anti-CD 20 monoclonal antibody rituximab has emerged as an acceptable alternative to cyclophosphamide for induction therapy of AV(5,6).

Azathioprine has traditionally been the preferred agent for maintenance therapy(7). However, this strategy remains inadequate, with approximately 33% of patients relapsing at 2.5 years and a significant burden of treatment-related adverse events(8). Similarly, rituximab induction without subsequent maintenance therapy leads to unacceptable relapse rates(9). To circumvent these shortcomings, strategies employing continuous B cell depletion with maintenance rituximab dosing have been attempted. In the largest study to date, we demonstrated that rituximab administered to maintain continuous B-cell depletion produces outstanding results with a 2 year major relapse rate of 5% and a survival that mirrors the general population(10). Furthermore, a recent randomized trial confirmed that maintenance therapy with rituximab administered every 6 months is superior to daily azathioprine(11).

Despite yielding promising outcomes, rituximab is also associated with a number of adverse events including infectious complications and late onset of neutropenia(9,12). Furthermore, the complications of continuous B cell depletion for extended durations are unknown. One of the major goals in the field is to utilize prolonged B cell depletion only in the subpopulation of patients where the risk of disease relapse outweighs the risk of treatment-related adverse events.
A rise in ANCA titers and reconstitution of B cells are promising biomarkers of impending disease relapse following treatment with rituximab(9,13,14). We therefore propose a randomized trial in which these two biomarkers are used to guide additional treatment in patients who have completed at least 2 years of successful rituximab maintenance therapy.

The ANCA Assay

Our group was the first to demonstrate the association of ANCA with the neutrophil serine protease, proteinase 3 (PR3)(15). Since this time, our group has conducted numerous studies regarding the use of the ANCA assay in the diagnosis and management of ANCA vasculitis. In one investigation, 100% of patients in clinical remission who sustained a fourfold rise in ANCA titer without receiving immunosuppression relapsed at mean time of 5.8 months(13).

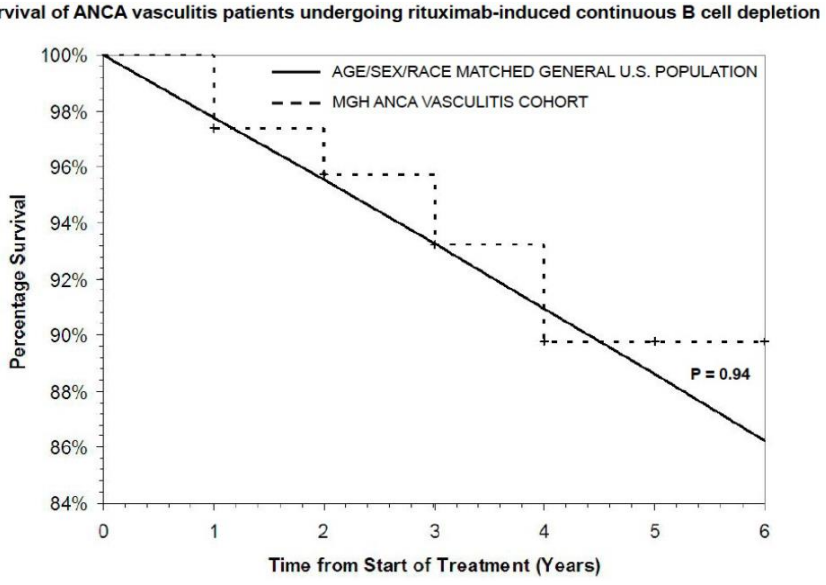
Rituximab for Maintenance Therapy in ANCA Vasculitis

Our group was one of the first to use rituximab as maintenance therapy for ANCA vasculitis in April of 2006. We subsequently reported that continuous B cell depletion using rituximab was highly successful for early maintenance of remission in 39 patients with ANCA vasculitis(16). This maintenance strategy was the first to use a regimen of scheduled rituximab administration in order to prevent B cell re-population.

We recently reviewed the long-term results of 172 ANCA vasculitis patients cared for by our group who underwent rituximab-induced continuous B cell depletion for maintenance of remission and found that remission was maintained in the majority of patients with a very low rate of major relapse. Most importantly, we found that this remission maintenance strategy appears to result in long-term survival matching that of the general U.S. population(10) (see Figure).

Relapse after Discontinuation of Rituximab

Data from randomized clinical trials and observational studies suggest relapse is common if rituximab is discontinued indefinitely. Among patients in the RAVE trial who achieved complete remission following treatment with rituximab, 32% had a relapse within 18 months(9). Furthermore, Alberici *et al* reported that 41% of patients who received maintenance rituximab every 6 months for 24 months relapsed at a median of 34.4 months following discontinuation of therapy(17). Predictors of relapse included return of B cells and change from ANCA negativity to positivity(17).



A prospective and longitudinal clinical trial is needed to determine the ideal treatment strategy for long-term maintenance of remission. Here we propose to compare 2 strategies once patients have

been in sustained remission on scheduled rituximab dosing with a goal of undetectable B cells for greater than or equal to 2 years. Target enrollment is 200 subjects over 48 months from the time the first patient is enrolled to be followed for a common close out date of 36 months after the last subject is enrolled.

The study design is an open-label, single center, randomized and two-arm controlled trial to evaluate the optimal maintenance of remission strategy that provides the best relapse-free survival in patients with ANCA vasculitis as determined by relapse-free remission at 18, 24 and 36 months from enrollment. Subjects with ANCA vasculitis in sustained remission on regularly scheduled rituximab infusions with a goal of undetectable B cells for a minimum of two years who meet specific entry criteria will be randomized with stratification based on ANCA subtype and rituximab vintage (i.e., duration of continuous rituximab prior to enrollment) to one of two arms :

1. **Intermittent B cell depletion with rituximab re-dosing upon B cell return:** Subjects will no longer receive regularly-scheduled every six-month doses of rituximab and will instead be seen in clinic with B cell monitoring every 3 months (beginning 6 months after their last rituximab dose). B cell levels will be determined by the number of CD20 positive cells detected by peripheral blood flow cytometry. Subjects will not receive rituximab if the B cell level remains < 10 cells/mm^3. Once peripheral B cells levels rise to $\geq$ 10 cells/mm^3, they will receive rituximab 1000 mg IV x 1 dose. If patients receive rituximab they will become B cell depleted, but will stay on their original study schedule. Following B cell depletion, subjects will be seen in clinic every three months, and B cell monitoring every 3 months will continue as scheduled. Patients will continue to be dosed with rituximab each time the B cell count rises to 10 cells/mm^3. In the unique scenario that the B cells are detectable, but less than the threshold of 10 cells/mm^3, subjects will be asked to return in 6 weeks for repeat B cell testing.

2. **Hold continuous dosing with rituximab with re-dosing upon significant ANCA titer increase:** Subjects will no longer receive regularly scheduled every six-month doses of rituximab, and will instead be seen in clinic with the ANCA titer monitoring every three months (beginning 6 months after their last rituximab dose). For MPO, a significant increase will be defined as a 5-fold rise in ANCA titer and a level greater than 4 times the cutoff value for the assay. For PR3, a significant rise will be defined as a 4-fold rise in ANCA titer to a level at least twofold above the cutoff value for the assay. Patients who sustain a significant increase in ANCA titer will receive rituximab 1000mg IV x 2 doses (~2-3 weeks apart). If the ANCA titer then falls to less than twofold above baseline or falls below the specified threshold (the cutoff value of the assay for PR3 and 4 times the cutoff value for MPO) after rituximab, patients will be seen in clinic every three months, with monitoring of ANCA titers. However, if the ANCA titer remains twofold above baseline and above the specified threshold (the cutoff value of the assay for PR3 and 4 times the cutoff value for MPO) after rituximab, patients will continue to receive rituximab 1000mg IV every 6 months for a maximum of 2 doses, at which time a new baseline ANCA titer will be established. Once the new baseline ANCA titer is established, the patients will continue to be seen in clinic every 3 months, with monitoring of ANCA titers. Patients will continue to be dosed with rituximab each time they meet criteria for a significant ANCA titer rise. In this arm, rituximab administration is not contingent upon B cell levels. Rituximab will only be dosed based on the ANCA titer as described above. Baseline ANCA titer will be recalculated to an average of the two highest of the last four values if all four are less than the original baseline. Patients in

the ANCA arm will move to once yearly CD20 testing after CD20 levels return to normal levels (>90 cells/uL).

Patients can be treated at any time during the study period with a total prednisone dose of ≤ 7.5 mg. Patients with a disease flare (defined by BVAS/WG ≥ 2) will have reached the primary endpoint and will be treated for relapse at the discretion of the investigator

II. Specific Aims

1. **Primary Aim: To determine whether a rituximab-dosing protocol based on: 1) reconstitution of peripheral B cells or 2)a serologic ANCA flare is more efficacious in preventing relapse in patients with ANCA vasculitis.** Eligible patients will have completed a minimum of 2 years of rituximab maintenance therapy without relapse. The endpoint will be disease relapse defined as a BVAS/WG ≥ 2. Analysis will also be stratified based on ANCA subtype (due to differences in relapse between patients with MPO and PR3 ANCA) and rituximab vintage.

2. **Secondary Aim 1: To determine whether a rituximab-dosing protocol based on: 1) reconstitution of peripheral B cells or 2) a serologic ANCA flare is associated with more serious adverse advents.** Serious adverse events of interest include those related to vasculitis activity and those that develop as a consequence of rituximab therapy. The main rituximab-associated serious adverse events noted in our cohort are infection, late-onset of neutropenia, and infusion reactions(10)

3. **Secondary Aim 2: To determine whether a rituximab-dosing protol based on: 1) reconstitution or peripheral B cells or 2) a serologic ANCA flare is associated with a greater composite of disease relapse (BVAS/WG ≥ 2) and serious adverse events.**

4. **Secondary Aim 3: To determine whether a rituximab-dosing protocol based on: 1) reconstitution of peripheral B cells or 2)a serologic ANCA flare is associated with greater rituximab utilization during the study period.** While effective, rituximab therapy is costly and increases health care expenditures. Evaluation of the relative cost of the 2 dosing-strategies will assist in the application of these dosing-strategies to the broad population of patients with ANCA vasculitis.

III. Subject Selection

Patients with ANCA vasculitis who are seen at MGH will be recruited as subjects and inclusion and exclusion criteria are detailed below.

A. Inclusion and exclusion criteria

Inclusion criteria:

1. All patients must be able and willing to give written informed consent and comply with the requirements of the study protocol.

2. Diagnosis: ANCA vasculitis as defined by a positive MPO- and/or PR3-ANCA test together with clinical features characteristic of ANCA-positive diseases as detailed in the 2012 Chapel Hill Consensus Conference Definitions(18).
3. eGFR ≥ 20 cc/min/1.73m^2
4. Age: 18-82 years old
5. Treated with continuous rituximab at regularly scheduled intervals with a goal of undetectable B cells for at least 24 months.
6. In sustained remission (defined by a modified BVAS-WG=0 **AND** a prednisone dose of ≤7.5mg for at least 12 months).
7. Undetectable (<10mm^3) B cells as quantified by the number of CD20+ cells on peripheral blood flow cytometry on day 0.
8. Urine Hcg negative for women of child bearing potential and not planning to become pregnant for at least 12 months from enrollment and at least 12 months after any study related rituximab dose
9. Judged to be otherwise healthy by the Investigator, based on medical history and physical examination (no known active disease process for which life expectancy is less than 36 months)

Exclusion criteria:

1. Secondary Disease: disease suspected to be induced by levamisole-adulterated cocaine
2. All transplanted patients
3. Treatment: additional immunosuppressive agents other than rituximab and/or total daily prednisone dose ≥ 7.5 milligrams
4. Hypogammaglobulinemia: IgG level < 300mg/dL
5. Terminal cancer or other primary illness with life expectancy of less than 36 months
6. Active anti-GBM disease and other known autoimmune disease for which the need for additional immunosuppression is likely
7. Pregnancy or breastfeeding

B. Sources of subjects and recruitment methods

Subjects will be recruited from the current pool of patients in the MGH Renal and Rheumatology Units of the Vasculitis and Glomerulonephritis Center.

IV. Subject Enrollment

A. Methods of enrollment

Patients will be prescreened for eligibility by research staff prior to their scheduled rituximab infusion. Potential subjects will be assessed for eligibility utilizing existing data regarding current length of treatment with rituximab, prednisone dose (if any) and most recent Birmingham Vasculitis Activity Score.

At a regularly scheduled clinic visit, study site personnel will assess a patient's eligibility for enrollment, including review of the inclusion and exclusion criteria. Patients meeting all the inclusion criteria and have no exclusionary criteria and receive treatment for their ANCA Associated Vasculitis by physicians in the MGH Renal and Rheumatology Unit's Vasculitis and Glomerulonephritis Center will be offered the opportunity to participate in this study as part of their ongoing treatment.

B. Procedures for obtaining informed consent

When a potential subject is identified, the research nurse will initially explain the study to the patient after their clinical visit with Dr. Niles, Dr. Cortazar, or Dr. Wallace. If the patient expresses further interest in participating in the study, Dr. Niles, Dr. Cortazar, or Dr. Wallace and the research nurse will then review the study details with the patient. The patient will be provided the opportunity to take the consent form home to further review and will follow-up with the research nurse or investigator within 14 days. If they decline participation, they will continue to receive their standard of care as deemed appropriate by their treating clinician. Massachusetts General Hospital is expecting to enroll up to 200 subjects over 36 months.

C. Treatment assignment and randomization

Each subject will be stratified prior to randomization to ensure MPO- and PR3-ANCA serotypes and duration of rituximab therapy are approximately equal within each arm. Randomization will occur using random permuted blocks to assign each subject to one of two arms:

1. Treatment upon B cell return, OR
2. Treatment upon a significant rise in ANCA titer as defined above.

V. Study Procedures

A. Study visits and parameters to be measured

1. Potential subjects will be identified during a clinical visit. Medical records will be reviewed by study staff and if found eligible then the potential subjects will be offered the opportunity to participate in the study at that visit. Potential subjects will have 14 days to decide on participation.
2. "Day 0" is defined as the date of the last rituximab infusion prior to randomization and must be 6 months +/- 14 days from Study visit 1. Existing data will be collected from this date once enrolled and randomized.
3. **Study Visit 1**: Enrollment and Randomization
    a. Patients who agree to participate and have signed and dated the consent form will be randomly assigned to one of two treatment arms:
        i. **Arm 1**: Subjects will not receive their regularly-scheduled dose of rituximab, but will be asked to return to clinic for a follow-up visit 6 months after their last rituximab infusion. Subjects will then receive blood work and scheduled clinic visits every three months thereafter. Once B cell return occurs, as defined as ≥ 10 cells/mm^3, subjects will be scheduled to receive rituximab 1000 mg IV x 1 dose. If a dose of rituximab is administered, the patient study schedule will not be adjusted. Patients will continue to be evaluated every three months per study protocol. If the B cells are detectable but <10 cells/m^3 , subjects will not be redosed, but will be asked to return in 6 weeks for repeat B cell monitoring.

            Arm 2: Subjects will not receive their regularly scheduled dose of rituximab, but will be asked to return to clinic for a follow-up visit 6 months after the last rituximab infusion. Subjects will then receive blood work and scheduled clinic

visits every three months thereafter. If the ANCA titer has increased above the threshold for treatment described above, then the patient will be re-dosed with rituximab 1000mg IV x 2 doses 2-3 weeks apart . If the ANCA titer remains twofold above baseline and above a specified threshold (the cuttoff value of the assay for PR3 and 4 times the cutoff value for MPO) , patients will continue to receive rituximab 1000mg IV every 6 months for a maximum of 2 additional doses, at which time a new baseline ANCA titer will be established. Subjects will continue to be evaluated every three months per protocol schedule.

b. A detailed history and physical examination will be performed along with the following disease assessment surveys and blood and urine measurements:
    i. Demographic characteristics
    ii. Date of initial physician's diagnosis of ANCA vasculitis
    iii. Length of continuous B cell depletion treatment
    iv. Medical history
    v. Vasculitis Damage Index (VDI) Score
    vi. Modified Birmingham Vasculitis Activity-WG (BVAS-WG) Score
    vii. Any adverse events since last infusion of rituximab
    viii. Prior and concomitant medications
    ix. Height and weight
    x. Blood work including but not limited to:
        1. Complete Blood Count
        2. Comprehensive Metabolic Panel
        3. eGFR
        4. ANCA titer
        5. ESR
        6. CRP
        7. Hep B sAg, Hep C Ab, HIV ½ (if not performed in the previous 12 months prior to screening and only at enrollemnt)
        8. Immunoglobulin levels
        9. Flow cytometric analysis of peripheral B and T cells
        10. Urinalysis
        11. Urine human chorionic gonadotropin (hCG) in women of child bearing potential
    xi. Quality of life surveys SF36 v2 and EQ 5D-5L
    xii. Baseline ECG
    xiii. Cough assessment/scale

4. Study Visits 2-16: Study visit 2 will occur at the 6 month time point from Day "0" (+/- 14 days) and subsequent visits will take place every three months (+/- 14 days) thereafter until a common close out date of 36 months after the last subject is enrolled.
    a. Subjects will be seen every three months in clinic and the same measurements will be performed as listed in the Enrollment and Randomization Visit.
        i. The VDI Score will only be calculated every other visit after Study visit 2 as this score is designed to measure cumulative damage every six months.
        ii. Subject quality of life assessments SF 36v2 and EQ-5D-5L will be assessed every 6 months from time of Study visit 2.

iii. ECG will be performed every 12 mos
iv. Adverse Events will be assessed at each visit
v. Cough assessment/scale

b. In cases where subjects need to come in for an infusion in between scheduled visits, the visit directly after the infusion may be done over the phone instead of coming in to the clinic. This will be decided at the discretion of the PI based on any hardships the patients may have related to distance of travel. The same measurements will be performed as an on-site visit (VDI score, BVAS, adverse events, and cough/assessment), except for the ECG and blood draw. The ECG will be added to the next office visit, and blood work will be deferred for that visit, and resumed at the next time point. Subject Quality of Life Assessments SF36v2 and EQ-5D-5L may be mailed to subjects for completion, then returned at the next office visit.
c. If subjects miss their scheduled visits and are unable to reschedule in window, a deviation will be filed and an investigator will call them to assess AEs and disease activity.
d. Subject visits can be completed as telemedicine with remote lab draws during the COVID-19 pandemic. Lab draws may be delayed up to 4 weeks at the investigator's discretion. A minor deviation will be filed if lab draws occur outside that window.

B. Drugs to be used

Rituximab (Rituxan, Genentech), which is FDA-approved for GPA and MPA, will be used in the study.

C. Devices to be used

Not applicable

D. Procedures/surgical interventions

Not applicable

E. Data to be collected and when the data is to be collected

At present, there is no standard of care for maintenance of remission in ANCA vasculitis beyond the two-year mark; thus, the role of continuous versus intermittent B cell depletion requires investigation. Efficacy and toxicity are the foci of our outcome analysis for this study and will be assessed through analysis of primary and secondary endpoints.

The following variables will be collected at EACH study visit:

1. VDI (every 6 months)
2. Modified BVAS/WG
3. Laboratory data at baseline and at subsequent visits
    a. Complete Blood Count
    b. Comprehensive Metabolic Panel
    c. eGFR
    d. ANCA titer
    e. ESR
    f. CRP

g. Immunoglobulin levels (every 6 months)
h. Urinalysis
i. Urine Hcg for women of child bearing potential (only at screening and when reinfused with rituximab)
j. Flow cytometric analysis of peripheral B and T lymphocyte markers

4. Concomitant medications at each visit
5. Adverse events assessment

VI. Biostatistical Analysis

A. Specific data variables being collected for the study (e.g. data collection sheets)

Data variables collected are listed above and we will also verify contact information at each visit to ensure appropriate follow-up.

B. Study endpoints

Primary endpoints:

1. Disease flare defined as a BVAS/WG ≥ 2. A subgroup analysis will be performed by ANCA subtype.

Secondary endpoints:

1. Proportion of patients with serious adverse events (SAEs), including all episodes of Late Onset Neutropenia (LON, absolute neutrophil count < 1000 cells/mm^3)
2. The composite of disease flare (defined as BVAS/WG ≥ 2) and serious adverse events.
3. Total rituximab utilization during the study period
4. Accrued organ damage as assessed by the Vasculitis Damage Index (VDI)
5. Patient quality of life assessment using the SF-36v2 and EQ-5D-5L surveys every 6 months
6. Number of major (modified BVAS-WG ≥ 3) relapses
7. Survival
8. Hypogammaglobulinemia (IgG < 400 mg/dL)
9. All infections

C. Statistical methods

Data will be analyzed by the intention-to-treat principle. Randomization will be stratified on ANCA subtype (MPO vs PR3) and rituximab vintage (< 3 years vs > 3 years). Rituximab vintage is the duration of continuous rituximab therapy administered prior to enrollment in the study. We have contracted with the company StudyTRAX to perform randomization on stratified variables via random permuted blocks.

Continuous data will be summarized using descriptive statistics. Continuous data will be assessed using the t-test or Wilcoxon rank-sum test as appropriate. Categorical data will be assessed using the Chi-square and the Fisher exact tests as appropriate. The probability of remaining free of relapse will be estimated using the Kaplan-Meier method. The difference between the two

treatment strategies will be assessed using the log-rank test. *P* values of 0.05 will be considered significant.

D. Power analysis

Using a two-sided logrank test with an alpha level of 0.05, a projected relapse risk of 15% in the superior group and 30% in the inferior group, and an estimated enrollment time of 36 months, it was determined that 180 patients are required to detect a significant difference with a power of 0.80. We aim to enroll 200 patients in the study.

VII. Risks and Discomforts

Subjects may experience side effects while receiving rituximab, which is given as part of their regular medical care for their GPA or MPA. As per the entry criteria, subjects have been on rituximab for 2 years prior to enrollment, the side effects have been discussed in detail and a signed consent for rituximab is obtained for every patient receiving rituximab at the first dose and annually thereafter.

The effects of rituximab on a fetus are unknown and may be harmful. Individuals of childbearing potential should use effective birth control during treatment and for 12 months after their last rituximab infusion. Prior to any infusion of rituximab to a woman of childbearing potential, a urine pregnancy test is performed and recorded. If a woman is found to be pregnant, she will then be removed from the study and followed based on best medical judgment as deemed appropriate by the clinician investigator.

A. Complications of surgical and non-surgical procedures

Not applicable

B. Drug side effects and toxicities

Common side effects of Rituxan

- Infusion reactions may be fatal. Serious infusion reaction with hives, low blood pressure, breathing difficulties, irregular heartbeat and chest pain are very rare. Medications given as pre mediction: Benadryl 25mg PO, tylenol 650mg PO and Solucortef 100mg IV, are always given and can prevent these reactions. We will temporarily stop the infusion immediately if a reaction occurs.
- Within 24 hours of the 1st infusion
    - Chills, itching, hives, sneezing, throat irritation
    - "flu like" symptoms: headache, nausea, joint pain

- Possible serious side effects or reactions that can occur at any time
    - Infections are a concern with all drugs that affect the immune system. If you develop a severe infection, we will check your labs including a complete blood count. This is always something that needs attention and treatment
    - Reactivation (getting symptoms again) of Hepatitis B and other viral infections. Hepatitis B Core is always checked at the screening or first visit.

- Worsening of asthma symptoms
- A rare brain infection, progressive multifocal leukoencephalopathy (PML), has been reported in people taking this medication. This infection is rare, associated with weakened immune systems, and can lead to death or severe disability.
- Skin reactions, painful sores, ulcers, blisters and peeling skin (rare)

There may be other risks of rituximab that are currently unknown.

As with any drug, the major possible side effect of rituximab can be an allergic reaction. Allergic reactions can be mild or more serious, and can even result in death.

Subjects cannot receive a live vaccine such as zostavax while receiving rituximab.

C. **Risk of relapse**

The discontinuation of maintenance rituximab will likely lead to an increase in disease relapse. Relapses have the potential to cause irreversible organ damage, resulting in significant morbidity. Particularly concerning is the potential for recurrence of rapidly progressive glomerulonephritis leading to ESRD and dialysis dependence. The risk of relapse must be weighed against the harms of ongoing treatment with immunosuppression. While no randomized clinical trials have been performed, standard of care is to continue maintenance therapy for 1-2 years. To mitigate the risk of significant morbidity from disease relapse, we have restricted entry to patients treated with maintenance therapy for a minimum of 2 years and excluded patients with an eGFR < 20 ml/min/1.73 m^2.

D. Device complications/malfunctions

Not applicable

E. Psychosocial (non-medical) risks

There are no known psychosocial risks associated with this study, however there may be unknown risks that will be addressed if they become known.

F. Radiations Risks

Not applicable

VIII. Potential Benefits

A. Potential benefits to participating individuals

There may not be any direct benefits to subjects who participate in this trial. Information learned by conducting this trial may benefit future patients by helping determine a long term plan with regards to rituximab administration for patients with GPA or MPA.

B. Potential benefits to society

This study, once completed, will be a landmark trial in the field of remission maintenance therapy for ANCA vasculitis. Currently, specialists do not know the ideal treatment strategy for this subset of patients and this study is likely to provide the answer. In addition, if it is found that either Arm 1 or Arm 2 are as effective as ongoing continuous therapy, there will be cost-effective benefit to society in that less rituximab will be required to maintain remission.

IX. Monitoring Quality and Assurance

A. Independent monitoring of source data

The PI on this study will be responsible for the data management, integrity of this data and adherence to the IRB-approved protocol. The PI will review the accuracy and completeness of entries, source documents, and informed consent on a regular basis.

Privacy of subjects will be protected and confidentiality of data collected maintained. All individually identifiable information will be stored in a secure, locked, location in the PI's office. Password-protected computer databases will be used with limited access to the study data. Files for data analysis will contain codes instead of identifiers. All identifiers will be removed once study is completed.

B. Safety monitoring

The patient's treating physician will be responsible for the treatment of any adverse events, in accordance with the approved product labeling and the physician's discretion.

Subjects will be withdrawn from the study at any point for the following reasons:

1. Serum IgG < 250 mg/dL at any point during the study.
2. Modified BVAS-WG ≥ 2
3. Require daily prednisone >7.5mg
4. WBC <3,000
5. Serious Infections that require hospitalization.

The investigators will also review the data every 6 months to ensure there are no safety concerns or clear inferiority in one arm that would warrant early termination of the trial.

C.Outcomes monitoring

The following outcomes will be collected throughout the study period as appropriate:

1. Disease flare defined as a BVAS/WG ≥2 (**primary aim**). A subgroup analysis will be performed by ANCA subtype.
2. Proportion of patients with serious adverse events (SAEs), including all episodes of LON.
3. Number of infections (mild and severe).
4. Total rituximab utilization during the study period.

5. Patient quality of life assessment using the SF-36v2 and EQ-5D-5L surveys every 6 months
6. Number of major (modified BVAS-WG ≥ 3) relapses
7. Survival
8. Hypogammaglobulinemia (IgG < 400 mg/dL)

D. Adverse event reporting guidelines

All adverse events will be reported per PHRC guidelines which includes unanticipated problems involving risks to subjects/others, including adverse events, within 5 working days/7 calendar days of the date that the investigator first became aware of the problem.

References

1. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. *Curr Opin Nephrol Hypertens* 20(3): 263-270, 2011

2. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS. Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 116(6): 488-498, 1992

3. Boumpas DT, Austin HA,3rd, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 119(5): 366-369, 1993

4. Huynh-Do U, Gantenbein H, Binswanger U. Pneumocystis carinii pneumonia during immunosuppressive therapy for antineutrophil cytoplasmic autoantibody-positive vasculitis. *Arch Intern Med* 155(8): 872-874, 1995

5. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR, European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 363(3): 211-220, 2010

6. 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, RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363(3): 221-232, 2010

7. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, Ekstrand A, Gaskin G, Gregorini G, de Groot K, Gross W, Hagen EC, Mirapeix E, Pettersson E, Siegert C, Sinico A, Tesar V, Westman K, Pusey C, European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349(1): 36-44, 2003

8. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, Kyndt X, Lifermann F, Papo T, Lambert M, Le Noach J, Khellaf M, Merrien D, Puechal X, Vinzio S, Cohen P, Mouthon L, Cordier JF, Guillevin L, French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 359(26): 2790-2803, 2008

9. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Fessler BJ, Ding L, Viviano L, Tchao NK, Phippard DJ, Asare AL, Lim N, Ikle D, Jepson B, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh K, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Mueller M, Sejismundo LP, Mieras K, Stone JH, RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 369(5): 417-427, 2013

10. Pendergraft WF,3rd, Cortazar FB, Wenger J, Murphy AP, Rhee EP, Laliberte KA, Niles JL. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. *Clin J Am Soc Nephrol* 9(4): 736-744, 2014

11. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, Quemeneur T, Blanchard-Delaunay C, Godmer P, Puechal X, Carron PL, Hatron PY, Limal N, Hamidou M, Ducret M, Daugas E, Papo T, Bonnotte B, Mahr A, Ravaud P, Mouthon L, French Vasculitis Study Group. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 371(19): 1771-1780, 2014

12. Tesfa D, Ajeganova S, Hagglund H, Sander B, Fadeel B, Hafstrom I, Palmblad J. Late-onset neutropenia following rituximab therapy in rheumatic diseases: Association with B lymphocyte depletion and infections. *Arthritis Rheum* 63(8): 2209-2214, 2011

13. Han WK, Choi HK, Roth RM, McCluskey RT, Niles JL. Serial ANCA titers: Useful tool for prevention of relapses in ANCA-associated vasculitis. *Kidney Int* 63(3): 1079-1085, 2003

14. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, Fervenza FC, Specks U. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (wegener's): Ten-year experience at a single center. *Arthritis Rheum* 64(11): 3770-3778, 2012

15. Niles JL, McCluskey RT, Ahmad MF, Arnaout MA. Wegener's granulomatosis autoantigen is a novel neutrophil serine proteinase. *Blood* 74(6): 1888-1893, 1989

16. Rhee EP, Laliberte KA, Niles JL. Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Clin J Am Soc Nephrol* 5(8): 1394-1400, 2010

17. Alberici F, Smith RM, Jones RB, Roberts DM, Willcocks LC, Chaudhry A, Smith KG, Jayne DR. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. *Rheumatology (Oxford)* 54(7): 1153-1160, 2015

18. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 65(1): 1-11, 2013