Tailoring Maintenance Therapy to CD5+ Regulatory B Cell Recovery in ANCA vasculitis: Protocol and statistical analysis plan

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Tailoring Maintenance Therapy to CD5+ Regulatory B Cell Recovery in ANCA vasculitis

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Rituximab,
Azathioprine
Mycophenolate mofetil

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Table of Contents

List of Abbreviations

ANCA	Anti-neutrophil Cytoplasmic Antibody
BVAS	Birmingham Vasculitis Assessment Score
CDA	Combined Damage Assessment Index
GN	Glomerulonephritis
MMF	Mycophenolate mofetil
PBMC	Peripheral Blood Mononuclear Cells
SD	Standard Deviation

Study Summary

Title	***TAILORING MAINTENANCE THERAPY TO CD5+ REGULATORY B CELL RECOVERY IN ANCA-VASCULITIS***
Short Title	***ANCA-VASCULITIS CD5+ B CELL TRIAL***
Protocol Number	**UNC IRB# 18-2015**
Phase	**Proof of Concept**
Methodology	***randomized, open label***
Study Duration	**4 years**
Study Center(s)	***Single-center***
Objectives	***To test the hypothesis that normalized CD5+ regulatory B cells repopulation after immunotherapy is associated with a decreased risk of subsequent relapse in ANCA vasculitis.***
Number of Subjects	***40***
Diagnosis and Main Inclusion Criteria	***ANCA GN or vasculitis patients in complete remission for at least one month and after 3 months of induction therapy.***
Study Product, Dose, Route, Regimen	***Rituximab 500 mg IV every 6 months*** ***OR Mycophenolate mofetil 1000 mg twice daily*** ***OR Azathioprine 1.5-2 mg/kg/daily once daily***
Duration of administration	**24 months**
Reference therapy	***Reference is no maintenance therapy.***
Statistical Methodology	***Proof of concept trial. As such, no statistical testing is planned, but trends, and estimates will be evaluated, described and used to provide sample size estimates and effect sizes for a future trial to advance this concept.*** ***The primary outcome measure is time to first relapse.*** ***Secondary outcome measures are 1) frequency and severity of relapse in each group and 2) time to positive ANCA test.***

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

ANCA vasculitis is a pauci-immune systemic small vessel vasculitis. The anti-neutrophilic cytoplasmic antibodies (ANCA) are pathogenic and cause disease by activating neutrophils which damage blood vessels. As their name suggests, ANCA are autoantibodies directed toward either of two neutrophil antigens myeloperoxidase (MPO) or proteinase 3 (PR3) (referred to as MPO-ANCA and PR3-ANCA respectively). Glomerulonephritis is seen in a majority of patients with ANCA vasculitis. Other organs may also be affected such as the lungs, upper respiratory tract, eyes, skin and peripheral nerves. ANCA vasculitis can be classified into one of 4 major clinical phenotypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), or pauci-immune glomerulonephritis without clinical evidence of extra-renal organ involvement (renal-limited disease).

ANCA vasculitis may be organ- and life-threatening in many cases. With early and appropriate therapy, the majority of patients attain a remission. Current standard induction therapy for ANCA vasculitis consists of a combination of corticosteroids with either cyclophosphamide OR rituximab. The adjunctive use of plasmapheresis is generally reserved to patients with severe diffuse pulmonary hemorrhage or severe renal failure. Such induction therapy is effective in inducing a remission in approximately 80% patients within a period of 6 months.

Over the last 20 years, great progress in induction therapy of ANCA glomerulonephritis (GN) and vasculitis resulted in a switch from 80% mortality to 80% induction of remission. This undeniable success, however, has shifted the main cause of mortality from underlying disease to complications of immunosuppression, most notably infections. Infections now represent the most common cause of death in patients with ANCA GN.

Disease relapse is unfortunately common especially among patients with PR3-ANCA. In addition, the existing options for both induction and maintenance therapy have substantial adverse effects and risks. The risks of continued immunosuppression with maintenance therapy must be weighed against the risk of relapsed disease. Minimizing complications of therapy rests in part on decreasing the duration of maintenance immunotherapy in patients who may be at decreased risk of relapse. There is no current agreed-upon standard for maintenance therapy in ANCA associated vasculitis (AAV). Various academic societies have provided suggested guidelines for continuing maintenance therapies with duration ranging from 18 months to 26 months (Geetha et al. KI Reports 2018: 3, 1039–1049). To date, there is no clear empiric data guiding the appropriate duration of maintenance therapy in patients with ANCA vasculitis. Further, there is no way of confidently identifying patients with low risk of relapse for whom maintenance immunotherapy may be reduced in duration or avoided altogether – thus reducing the adverse risks associated with it.

We previously detected an association between recovery of IL-10-secreting CD20+ and CD5+ regulatory B cells after immunotherapy (with rituximab and corticosteroids) and decreased risk of subsequent relapse in patients with ANCA-vasculitis. We hypothesize that patients with complete reconstitution of a functional regulatory B cell repertoire after induction therapy are at low risk of relapse and may be monitored conservatively without further immunotherapy. We will test this hypothesis through a proof of concept randomized controlled study. Patients with normalization of CD5+ regulatory B cells will be randomized to maintenance therapy with rituximab vs. close observation without immunosuppression. Patients whose peripheral CD5+ regulatory B cells remain low after induction therapy (who are at higher risk of relapse), will receive maintenance immunosuppression with rituximab. Patients needing or randomized to maintenance therapy who are unable to receive rituximab will receive azathioprine or mycophenolate mofetil, two standard alternative medications for maintenance immunosuppression.

1.1 Background

We recently demonstrated that B cells from patients with active ANCA GN express low levels of CD5, a surface molecule which negatively regulates B cell signaling through the B cell receptor (Bunch DO et al. Clin J Am Soc Nephrol 2013;8(3):382-91). In contrast, patients who are in remission have CD5+ B cell levels comparable to those in healthy individuals. Moreover, after induction treatment with rituximab, we found that patients with low or declining levels of CD5+ B cells (at the time of repopulation of peripheral B cells) have a greater likelihood of subsequent relapse. In mice, CD5+CD1dhi B cells secrete IL-10 and have a regulatory function evidenced by their inhibition of IFN-γ and TNF-α expression in T cells (Yanaba K et al. Immunity 2008;28(5):639-50). IL-10-producing regulatory B cells have been described in humans; however, their phenotype remains incompletely characterized. We have demonstrated that the CD5+ subset of CD24hiCD38hi B cells decreases in active disease and rebounds during remission similarly to IL-10 producing B cells suggesting that CD5 may identify functional IL-10 producing B cells (Aybar LT et al. Clin Exp Immunol. 2015;180(2):178-88. As IL-10 producing B cells and CD5+CD24hiCD38hi B cells increase during remission within an individual, ANCA titers decrease. These data indicate that B regulatory cells malfunction during active disease due to reduced IL-10 expression, thus permitting ANCA production. In a *post hoc* analysis of the RAVE-ITN trial of rituximab versus cyclophosphamide induction treatment in ANCA vasculitis (Stone JH et al. N Engl J Med 2010;363:221–32.), a statistically significant inverse correlation between disease activity and the relative number of CD5+ B cells was detected in patients who received induction treatment with rituximab, but not among patients who received induction with cyclophosphamide followed by maintenance treatment with azathioprine (Unizony S et al. Arthritis Rheumatol. 2015;67(2):535-44). In this study, no association between percent CD5+ B cells at the time of peripheral B cell detection and the time-to-relapse could be demonstrated. In an independent cohort of 50 patients with ANCA vasculitis, we determined B cell phenotype after rituximab therapy and confirmed our finding that patients who repopulated with ≤30% (low) CD5+ B cells relapsed sooner than patients who repopulated with high CD5+ B cells (p=0.001) (Bunch DO et al. Ann Rheum Dis. 2015;74(9):1784-6.). Controlling for upper respiratory involvement and PR3-ANCA serotype, known risk factors for relapse, patients with low CD5+ B cells remained at higher risk for relapse with a hazard ratio (HR) of 3.7 (95% CI 1.5 to 9.0, p=0.005). For this study, data from UNC McLendon Clinical Flow Cytometry Laboratories was reanalyzed to determine the percent of CD5+ B cells instead of CD5+ lymphocytes typically reported in this clinical test. We are proposing a similar analysis to determine CD5+ B cells in this application.

The goal of this study is to test the hypothesis that use of CD5+ B cells at the time of B cell reconstitution in the peripheral blood can be used to stratify patients between those with low % CD5+ B cells at greater risk of relapse who would need maintenance immunosuppression and those with normalized CD5+ B cells who would be at lower risk and relapse, and therefore may not need maintenance immunosuppression. The latter group will be randomized to either maintenance immunosuppression vs close clinical observation without maintenance immunosuppression. This study is not designed to evaluate the efficacy of new therapies in ANCA vasculitis. The treatment regimen used in the proposed study are routinely used in the treatment of patients with ANCA vasculitis and considered standard-of-care.

<u>Proof of concept:</u>
We will evaluate if the concept of stopping maintenance therapy and participation in the trial with randomization based on low (but not zero) risk of disease relapse based on a novel marker is acceptable to patients. Once in the study, we will evaluate relapse and other outcomes to use in estimating sample size for a larger study. In addition to the study outcomes described, we will evaluate the following:

- the number who are eligible but choose not to enroll and their reason for declining.
- once enrolled, how many patients terminate early from the study and why.

These data will inform the feasibility and needs to move forward with a larger definitive study and allow a subsequent study to be tailored to be acceptable to patients. If our “Stopping Rules” (see below) are met, we would be cautious about developing a new trial with this marker and its defined cutoff.

1.2 Investigational Agents

This clinical trial is not aimed at testing the efficacy of investigational agents in ANCA vasculitis. Rather, it will test whether measuring the % CD5+ B cells at the time of B cell recovery in the periphery can help stratify patients between those at greater vs lower risk of relapse. All the medications used in this trial (rituximab, azathioprine, or mycophenolate mofetil) are FDA approved and currently routinely used in the maintenance therapy of patients with ANCA-vasculitis. Rituximab is FDA approved for the treatment of GPA. While Azathioprine and mycophenolate mofetil are not labeled for treatment of ANCA vasculitis, they are routinely used off label in maintenance therapy of this disease.

Subjects assigned to treatment groups will receive rituximab for maintenance therapy unless they are intolerant or allergic to rituximab or cannot access it (e.g. insurance coverage) in which case they will receive azathioprine or mycophenolate mofetil. These FDA approved drugs are prescribed at UNC for maintenance therapy as part of standard care maintenance therapy for the majority of patients with ANCA vasculitis (the patient population in this study).

Rituximab (Rituxan), which received initial U.S. approval in 1997, is a genetically engineered murine/human monoclonal IgG kappa antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. Upon binding to CD20, rituximab mediates B cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T cell activation, and/or proinflammatory cytokine production.

Warnings:

Infusion Reactions:
Rituximab administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion.

Severe Mucocutaneous Reactions:
Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab.

Hepatitis B Virus (HBV) Reactivation:
HBV reactivation can occur in patients treated with Rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving Rituxan

Most common adverse reactions in clinical trials were:

- Non-Hodgkins Lymphoma (≥ 25%): infusion reactions, fever, lymphopenia, chills, infection and asthenia (6.1).
- Chronic lymphocytic leukemia (≥ 25%): infusion reactions and neutropenia (6.1).
- Rheumatoid Arthritis (≥ 10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion reactions, serious infections, and cardiovascular events) (6.2).
- Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA) (≥15 %): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (other important adverse reactions include infusion reactions) (6.3).

For more information, please see the full prescribing information at:
http://www.gene.com/download/pdf/rituxan_prescribing.pdf

Azathioprine (**Imuran**) is an immunosuppressive antimetabolite used in organ transplantation and autoimmune diseases and belongs to the chemical class of purine analogues. Synthesized originally as a cancer drug and a prodrug for mercaptopurine in 1957, it has been widely used as an immunosuppressant for more than 50 years. Azathioprine is used alone or in combination with other immunosuppressive therapy to treat an array of autoimmune diseases, including vasculitis.

WARNING: MALIGNANCY Chronic immunosuppression with Imuran increases risk of malignancy in humans. Reports of malignancy include post-transplant lymphoma and hepatosplenic T-cell lymphoma (HSTCL) in patients with inflammatory bowel disease.

The principal and potentially serious toxic effects of Imuran are hematologic and gastrointestinal. The risks of secondary infection and malignancy are also significant. The frequency and severity of adverse reactions depend on the dose and duration of Imuran as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing Imuran for rheumatoid arthritis. The relative incidences in clinical studies are summarized below:

Toxicity	**Renal Homograft**	**Rheumatoid Arthritis**
Leukopenia (any degree)	>50%	28%
<2500 cells/mm3	16%	5.3%
Infections	20%	<1%
Neoplasia		*
Lymphoma	0.5%	
Others	2.8%	

Most common adverse reactions: nausea, vomiting, diarrhea, loss of appetite, rash, hair loss, fever, weakness, and muscle pain.

For additional information, please see the full prescribing information at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf

Mycophenolate Mofetil: (CellCept): Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for MMF is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of C23H31NO7 and a molecular weight of 433.50.

MMF has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). MMF has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. MMF also inhibited proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats, as well as in primate cardiac xenografts. MMF was used alone or in combination with other immunosuppressive agents in these studies. MMF has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

MMF is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific

stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. MMF did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Warnings:

Pregnancy and Fetal Harm:
MMF can cause fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney and nervous system. Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Lymphoma and Malignancy
Patients receiving MMF as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving MMF (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients.

Serious Infections
Patients receiving immunosuppressants, including MMF, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal outcomes.

New or Reactivated Viral Infections
Polyomavirus associated nephropathy (PVAN), JC virus associated progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including MMF. PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft.

Neutropenia
Severe neutropenia [absolute neutrophil count (ANC) <0.5 x 103/µL] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving MMF 3 g. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or some combination of these causes. Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection.

Pure Red Cell Aplasia (PRCA)
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy.

Adverse Reactions:
The principal adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections e.g., opportunistic. The adverse event profile associated with the administration of MMF Intravenous has been shown to be similar to that observed after administration of oral dosage forms of MMF.

For more information on MMF, please see the full prescribing information at:
http://www.gene.com/download/pdf/cellcept_prescribing.pdf

1.3 Clinical Data to Date

Rituximab:

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
A total of 197 patients with active, severe GPA and MPA (two forms of ANCA Vasculitis) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases—a 6-month remission induction phase and a 12-month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus Conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease. Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either Rituxan 375 mg/m2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6-month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. The study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months.

Complete Remission (CR) at 12 and 18 months
In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment with Rituxan
Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the first course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent

courses of Rituxan in patients with GPA and MPA [*see Warnings and Precautions (5.14)*].

For information on azathioprine, please see:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf

For information on Mycophenolate Mofetil, please see:

http://www.gene.com/download/pdf/cellcept_prescribing.pdf

1.4 Dose Rationale and Risk/Benefits

B cells are commonly identified by the presence of either CD20 or CD19. Developmentally, CD19 is expressed earlier than CD20 and continues to be expressed after CD20 expression is lost during B cell differentiation to plasma cells. To maximize detection of B cells, we will employ CD19 in flow cytometric analysis of CD5+ B cells.

Patients whose CD5+ B cells account for 43% or greater of total CD19 B cells will be randomized to either NO maintenance therapy or to maintenance therapy with rituximab 500 mg IV every 6 months starting when the CD19+ B cells are >= 1% of total lymphocytes (and CD5+ B cells are measurable) and at least 4 weeks after the last dose of cyclophosphamide (for patients who received cyclophosphamide induction therapy). Patients who are allergic or intolerant to rituximab or cannot access rituximab (e.g. insurance reasons) will receive maintenance therapy with azathioprine 1.5-2 mg/kg/day or mycophenolate mofetil 1000 mg twice daily (or equivalent). The B cell cut off level was selected to provide a conservative selection of patients with high level of CD5+ B cells, who would be at low risk of subsequent relapse.

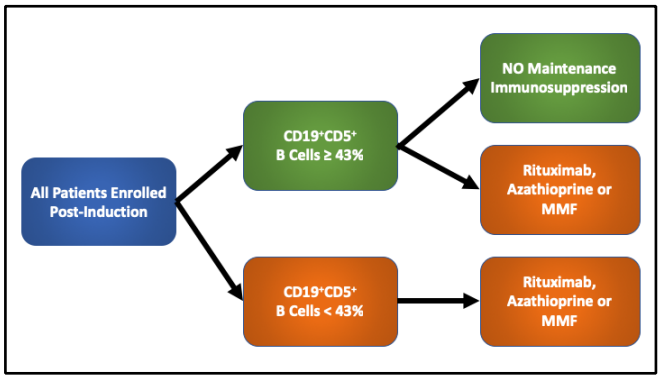
Patients whose CD5+ B cells remain < 43% of total CD19 B cells will receive maintenance therapy with rituximab 500 mg IV every 6 months starting when the CD19+ B cells are >= 1% of total lymphocytes (and CD5+ B cells are measurable) and at least 4 weeks after the last dose of cyclophosphamide (for patients who received cyclophosphamide induction therapy). [Guillevin L et al 2014]. Patients who are allergic or intolerant to rituximab or cannot access rituximab (e.g. insurance reasons) will receive maintenance therapy with azathioprine 1.5-2.0 mg/kg/day or mycophenolate mofetil 1000 mg twice daily.

2 Study Objectives

The primary outcome measure is time to first relapse defined as recurrence of any signs or symptoms attributable to active vasculitis after a period of complete remission with at least 2 minor or 1 major item on the BVAS score (BVAS≥2). Secondary outcome measures are 1) frequency and severity (as determined by BVAS score) of relapse in each group; 2) time to positive ANCA; 3) frequency and severity of infections; 4) time to IL-10 secreting B regulatory cells > 45% or CD5+ B cells > 43% of total B cells.

3 Study Design

3.1 General Design



A total of 40 patients will be enrolled in the end of induction therapy if they meet the inclusion/exclusion criteria defined below.

- Patients who recover > 43% CD5+ total B cells) will be randomized to maintenance therapy (WATCH maintenance therapy with rituximab every 6 months starting when the cells are > =1% of total lymphocytes cells are measurable) and at least 4 the last dose of cyclophosphamide who received cyclophosphamide induction therapy). Patients who are allergic or intolerant to rituximab

study at the B cells (of either NO group) or 500 mg IV CD19+ B (and CD5+ B weeks after (for patients

or cannot access rituximab (e.g. insurance reasons) will receive maintenance therapy with azathioprine 2 mg/kg/day or mycophenolate mofetil 1000 mg twice daily. These cut off levels were selected as they represent 2 standard deviations (SD) above the mean for healthy controls. This will provide a conservative selection of patients with high level of CD5+ B cells, who would be at low risk of subsequent relapse.

- Patients whose CD5+ B cells remain < 43% will all receive maintenance therapy with rituximab 500 mg IV every 6 months starting after the CD19+ B cells are >= 1% and at least 4 weeks after the last dose of cyclophosphamide the last dose of rituximab or cyclophosphamide or no maintenance immunosuppression. Patients who are allergic or intolerant to rituximab or cannot access rituximab (e.g. for insurance reasons) will receive maintenance therapy with azathioprine 2 mg/kg/day or mycophenolate mofetil 1000 mg twice daily.
- All patients in the WATCH group will be seen in clinic every 4 weeks for the first four months and then every 6 weeks for a total of 24 months of follow-up from enrollment. All patients in the Maintenance Therapy group will be seen in clinic every 8-12 weeks , as decided by treating nephrologist, for a total of 24 months of follow-up from enrollment These follow-up schedules correspond to our standard of care for patients with de novo, or relapsing ANCA GN and vasculitis.

Enrollment and subsequent randomization will occur when peripheral B cells (CD19+) are detected at >=1% of the total lymphocyte count, the threshold above which it is possible to reliably quantify CD5+ B cells. Treatment group assignment and randomization will be based on measures of CD5+ B cells.

B cell subsets will be measured in the UNC Hospitals clinical lab as per our standard of care after treatment with rituximab. We will measure % of CD19+ y flow cytometry. A sample will be obtained for research analysis with each clinical sample to determine the %CD19+CD5+ B cells. For study inclusion, we will require a minimum threshold of 50 CD5+CD19+ ***total detectable*** events to assess this percentage. In the WATCH group, the first sample will be obtained at the time of enrollment, 6, and 12 weeks later and then at every visit subsequently until CD19+ B cell are >=1%. . In the maintenance therapy group, B cell subsets will be measured at the time of enrollment, and prior to each Rituximab infusion until Month 24. For subjects on maintenance therapy with azathioprine or mycophenolate mofetil, B-cell subsets will be measured at enrollment, week 22, week 46, week 70 and week 94.. Detailed B cell phenotyping and measure of IL-10 production will be performed at the same time as CD5+ analysis.

3.2 Primary Study Endpoints

Primary outcome measure is time to first relapse - defined as recurrence of any signs or symptoms attributable to active vasculitis consisting of at least 2 minor or 1 major item on the BVAS score (BVAS ≥2) - after a period of complete remission.

3.3 Secondary Study Endpoints

Secondary outcome measures are 1) frequency and severity (as determined by BVAS score) of relapse in each group; 2) time to positive ANCA; 3) frequency and severity of infections; 4) time to relapse after IL-10 producing B cells > 45% of total B cells, compared to when CD5+ B cells are > 43% of total B cells.

3.4 Primary Safety Endpoints

The primary safety endpoint will be time to relapse after randomization as defined above.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Patients 18-85 years old.

- ANCA GN or vasculitis per Chapel Hill Consensus Criteria, with documented current or previously positive MPO- or PR3-ANCA by ELISA test. Patients with biopsy-proven, pauci-immune crescentic glomerulonephritis are eligible if they have a positive ANCA test by immunofluorescent microscopy (IIFM).
- Patients must be in complete remission for at least 1 month and after AT LEAST 3 MONTHS of induction of therapy with corticosteroids and rituximab (either 1000 mg IV x 2 or 375 mg/m2 IV x 4) OR corticosteroids and cyclophosphamide (monthly IV or daily oral doses). They must be on no more than 5 mg daily of oral prednisone or equivalent. Complete remission is defined as a BVAS score = 0.
- Patients may be ANCA negative or positive at enrollment.
- B cells are not depleted anymore: B cell recovery reaches 1% CD19+ B cells (enough to allow determination of CD5+ B cells with confidence).

4.2 Exclusion Criteria

- Patients who have had ≥ 2 relapses (defined as recurrence of any signs or symptoms attributable to active vasculitis) previously as patients with multiple prior relapses may be at higher risk of future relapse and require maintenance therapy
- Patients with persistent low-grade disease activity ("grumbling" disease defined as BVAS > 0 and ≤ 3)
- Patients with active systemic infections or deep space infections within the 3 months prior to screening.
- Patients participating in another clinical trial mandating maintenance therapy
- Patients with drug-induced ANCA vasculitis (e.g. levamisole-adulterated cocaine)
- Active tuberculosis, human immunodeficiency virus (HIV), hepatitis C virus or hepatitis B virus infections
- For women of child-bearing potential, pregnancy, breastfeeding, unwillingness or inability to comply with effective contraception
- Inability to come to scheduled visits

4.3 Subject Recruitment and Screening

Subjects will be recruited from the UNC Kidney and Hypertension Clinic, located in the Ambulatory Care Center at UNC-Chapel Hill. Screening will be done by the designated study coordinator in concert with the principal investigator or clinical co-investigators (MDs).

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects, Data Collection and Follow-up for Withdrawn Subjects

We will withdraw subjects from the study if a subject asks to be withdrawn or if a subject does not adhere to the scheduled study visits or procedures. If a patient assigned to receive maintenance therapy decides to discontinue receiving therapy, the therapy will be discontinued but we will continue following the patient and collecting data and information about the subject for the full follow up period of 24 months after randomization. If a patient in the NO maintenance therapy group shows signs of disease relapse and needs immunosuppressive therapy, s/he will be started on treatment as determined by the treating physician but we will continue to collect data and information about the subject for the full follow up period of 24 months after randomization. If a subject becomes pregnant, she will be referred to her obstetrician and will be offered to be followed with the UNC High Risk Obstetrics clinic. The managing nephrologist will decide on her care plan with respect to treating the vasculitis if it is active. If she is on treatment with rituximab or MMF, she will need to discontinue these medications. The risks/benefits of continued maintenance therapy with azathioprine will be evaluated by the treating nephrologist and obstetrician. Regardless of therapy decision, we will continue to follow her for the full follow up period.

5 Study Drug

5.1 Description

See section 1.2

5.2 Treatment Regimen

See section 1.4

5.3 Method for Assigning Subjects to Treatment Groups

All subjects whose CD5+ B cells account for less than 43% of total CD19 B cells will be assigned to maintenance therapy. Those subjects with CD5+CD19+ B cells ≥ 43% will be randomized as follows:

Randomization Method

The randomization scheme will be held in ordered closed envelopes by the statisticians (Hogan and Hu), so once organized and numbered, they will not have the randomization visible. Study clinicians and coordinators will not have access to the envelopes and will call for the random assignment once a patient has signed consent and all study information is in place and ready for treatment assignment. In the rare event Dr. Hogan and Ms. Hu will not be available, another individual without direct involvement in the care of the patient will have instructions and envelopes to accept the call and relay the treatment assignment. Once assigned, the clinician and coordinator will provide a study ID to be placed on the study randomization assignment.

Randomization will be done in blocks of four to assure accrual of a balanced number of subjects in each of the two treatment groups. To balance the strongest risk factors for relapse, PR3 versus MPO-ANCA and those with versus those without a history of lung involvement during disease activity, we will create randomization schema separately for these strata (PR3 with lung disease, PR3 without lung disease, MPO with lung disease, MPO without lung disease). Patients with pauci-immune crescentic GN who are MPO and PR3 negative will be placed in the MPO-ANCA strata.

Therefore, assigning the two arms as A and B with the six possible 4-block combinations: 1) ABBA, 2) ABAB, 3) AABB, 4) BBAA, 5) BABA, 6) BAAB), the list of random blocks will be generated for each stratum resulting in a random order of blocks 1 through 6 by strata. Study personnel will assess the stratum assignment when patients are ready to be randomized, and then assign the random treatment arm accordingly. Example:

Random block assignments (10 blocks per strata to accommodate the unlikely event of a maximum of all 40 patients in a single strata):

PR3 + Lung: 4, 1, 2, 6, 5, 5, 4, 3, 2, 1
PR3 no Lung: 2, 1, 4, 6, 1, 4, 3, 3, 6, 1
MPO + Lung: 3, 6, 2, 2, 1, 3, 4, 5, 1, 2
MPO no Lung: 2, 2, 1, 5, 3, 4, 1, 1, 2, 5

The assignments for the first two blocks within each stratum are shown below:

	PR3 + Lung	PR3 no Lung	MPO + Lung	MPO no Lung
Random block:	**4**	**2**	**3**	**2**
Subject 1 by strata	B	A	A	A
Subject 2 by strata	B	B	A	B
Subject 3 by strata	A	A	B	A
Subject 4 by strata	A	B	B	B
Random block:	**1**	**1**	**6**	**2**
Subject 5 by strata	A	A	B	A
Subject 6 by strata	B	B	A	B
Subject 7 by strata	B	B	A	A
Subject 8 by strata	A	A	B	B

Maintenance Therapies

Rituxan

A prescription for the drug will be written by the nephrologist managing the subject's care and will be arranged with a UNC infusion center. The physician will discuss the drug with the subject and provide a printout of information about the drug. The drug will be administered as described below at a dose of 500mg.

Preparation and Administration of Study Drug

The preparation of rituximab for infusion will be performed by the UNC hospitals pharmacy according to their standard operating procedures for clinical use.

Step 1. Insert PIV
Step 2. Flush line with sodium chloride 0.9% 10 mL
Step 3. Administer premeds acetaminophen 650 mg orally and diphenhydramine 25 mg orally.
Step 4. Infuse rituximab 500 mg in sodium chloride (NS) 0.9% 500 mL IVPB started at 50/mg/hour; rate increase done, and vitals monitored according to protocol for 1st dose (see doc flowsheet).
Step 5. Flush line with sodium chloride 0.9% 10 mL
Step 6. Remove PIV; apply pressure and wrap infusion site.
Step 7. Ensure that patient is having no ill effects of the treatment and discharge from clinic.

HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C−8°C (36°F−46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Mycophenolate Mofetil

A prescription for the drug will be written by the nephrologist managing the subject's care and will be sent to the pharmacy of the subject's choice. The physician will discuss the drug with the subject and provide a printout of information about the drug. Patients are typically started at a dose of mycophenolate mofetil 500 mg ((or equivalent dose of mycophenolic acid) twice daily and the dose is titrated up to 750 mg twice daily after 2 weeks and again to 1000 mg twice daily 2 weeks later based on patients' tolerability. The drug will be taken orally and self-administered by the patient. The patient will take the drug on an empty stomach at least 1 hour before or 2 hours after a meal and will swallow it whole. The subject will be instructed to store the drug at room temperature (59° to 86°F) away from moisture and heat and to keep the bottle tightly closed.

HOW SUPPLIED

250 mg capsule

Blue-brown, two-piece hard gelatin capsules, printed in black with "CellCept 250" on the blue cap and "Roche" on the brown body.

500 mg tablets

Lavender-colored, caplet-shaped, film-coated tablets printed in black with "CellCept 500" on one side and "Roche" on the other.

Mycophenolate mofetil is also available in generic formulation.

Azathioprine

A prescription for the drug will be written by the nephrologist managing the subject's care and will be sent to the pharmacy of the subject's choice. The physician will discuss the drug with the subject and provide a printout of information about the drug. The subject will be instructed to take a dose equivalent to 1.5-2 mg/kg once a day. The drug will be taken orally and self-administered by the patient. The patient will take the drug with food. The subject will be instructed to store the drug at room temperature (59° to 86°F) away from moisture and heat and to keep the bottle tightly closed.

HOW SUPPLIED:

50 mg overlapping circle-shaped, yellow to off-white, scored tablets imprinted with "IMURAN" and "50" on each tablet. Azathioprine is also available in generic formulation.

5.4 Subject Compliance Monitoring

For patients assigned to receive maintenance therapy:

We will schedule infusion clinic visits for patients who will receive rituximab therapy and we will reschedule any missed infusion visits to ensure that they receive treatment.

We will ask patients taking mycophenolate mofetil or azathioprine questions about medication adherence at each visit and emphasize the importance of taking their medication as prescribed.

5.5 Prior and Concomitant Therapy

At the time of enrollment, all patient will have received induction therapy with corticosteroids in combination with cyclophosphamide or rituximab as described above. The choice of therapy (rituximab or cyclophosphamide), doses and number for doses and dates of infusions will be recorded. The number doses and number of doses of pulse methylprednisolone at the beginning of induction, as well as the doses and tapering schedule of daily oral prednisone will likewise be recorded.

For patients enrolled after induction treatment for relapsing vasculitis, the history of prior immunosuppressive therapy doses and dates will be extracted from the medical history or patient's record as available.

We will record all medications that subjects are currently taking at each visit from enrollment to the final follow up visit. We will record the name of each drug, dosage, frequency, start date, end date, and indication.

Which concomitant medicines/therapies (including rescue therapies) are permitted during the study

Use and choice of prophylactic antibiotics will be left to the treating physician's decision, with no identified restrictions.

Which concomitant medicines/therapies are not permitted during the study (if applicable)

Then use of maintenance oral cyclophosphamide, or the concomitant use of more than 1 maintenance immunosuppressant will not be allowed (e.g. rituximab + mycophenolate mofetil, or rituximab + azathioprine) will not be allowed. **Maintenance dose of prednisone cannot exceed 5 mg daily.** Patients requiring increased dose of prednisone, or combination immunosuppressant drugs will be deemed in relapse and to have reached the study endpoint. They will be withdrawn from the treatment protocol and followed for data collection only**.**

Note about live vaccines: Patients who are candidates for enrollment in the study will all have already received immunosuppressive therapy, and should not have received any live vaccine since the start of their immunosuppressive therapy. Should a patient have received a live vaccine in the 4 weeks prior to, or after enrollment, any maintenance immunosuppression for the prophylaxis against relapse (i.e., while the patient is clinically in remission) will be delayed for 4 weeks after the administration of the vaccine.

5.6 Packaging

The UNC pharmacy will mix IV bags for rituximab infusions.

Azathioprine and mycophenolate mofetil will be packaged in pill bottles used by commercial pharmacies to dispense drugs.

5.7 Receiving, Storage, Dispensing and Return

The UNC Infusion Clinic will receive a pre-mixed rituximab IV bag from the UNC pharmacy on the day on which it will be administered. The bag will not be stored or returned.

Subjects taking MMF or azathioprine will receive the drug from the pharmacy of their choice. They will be instructed to store the drug at room temperature (59° to 86°F) away from moisture and heat and to keep the bottle tightly closed. Patients will be instructed to take leftover medication to their pharmacy for safe disposal.

5.7.1 Receipt of Drug Supplies

N/A

5.7.2 Storage

N/A

5.7.3 Dispensing of Study Drug

The UNC Infusion Clinic will receive a pre-mixed rituximab IV bag from the UNC pharmacy on the day on which it will be administered. The bag will not be stored or returned.

Subjects taking MMF or azathioprine will receive the drug from the pharmacy of their choice.

6 Study Procedures

Pre-Screening: Potential subjects will be identified by reviewing the medical records of patients being seen in the UNC Kidney and Hypertension Clinic.

Enrollment Visit: The research coordinator (RC) will identify patients who meet inclusion/exclusion criteria. If an identified patient's regular nephrologist is not a member of the study team, the RC will first contact that physician to obtain permission to approach the patient. The RC will meet with an identified/approved patient during a regularly scheduled clinic appointment in the UNC Kidney and Hypertension Clinic to discuss the study. The RC will provide an overview of the study to ascertain the patient's interest in participating. If interested, the RC will review the ICFs with the patient, providing ample time for the patient to review the forms and ask questions. If the patient has questions to ask a physician, a physician member of the study team will meet with the patient, discuss the study, and answer questions. If the patient decides to enroll in the study, s/he will be asked to sign the ICFs. The RC will make copies of the ICFs to give to the patient.

The patient will have a physical examination, which will include a Birmingham Vasculitis Activity Score (BVAS). If the patient has been seen within 2 weeks prior with a physical exam performed for SOC, this examination and the BVAS calculated at that visit may be used for enrollment data. The RC will collect information about demographics and concomitant medications from the subject. The subject will be asked to complete a quality of life (QOL) questionnaire. We will draw 24 ml of blood for research tests when the subject has blood drawn for routine labs. We will record the results of certain routine labs (creatinine, urinalysis, CBC, and ANCA tests), as well as results from the B cell tests in our study database.

After enrollement and obtention of CD5+ levels, subject will be assigned to receive maintenance therapy (low CD5+ B cell recovery <43%) or be randomized to either receive or not receive maintenance therapy (high CD5+ B cell recovery ≥43%).

6.1. Subjects randomized to NO-maintenance therapy: the WATCH group

The subjects randomized to no-treatment will be followed up very closely:

Subjects will have study visits every 4 weeks for the first four months and then every 6 weeks for a total of 24 months of follow-up from randomization. The first visit after randomization will be Visit 1. Visit 1 will be scheduled as soon as possible after randomization.

Subjects will be called by phone by a study coordinator, nurse or physician between each clinic visit for a review of their clinical history to detect any symptoms or signs suggestive of relapse of vasculitis. Should the patient report a symptom or sign suggestive of relapse, she/he will be seen in clinic within the following week for full evaluation. The phone call will be done about 14 days after the clinic visit for the first four months and about 3 weeks after the clinic visit once the subject is followed every 6 weeks. The phone call will be done within a +/- 5 days window. Subject will be trained on the symptoms to watch for and instructed to call study team if such a symptom occurs, without waiting for study phone call or study visit.

Study visits will take place either in the UNC Kidney and Hypertension Clinic, at the Clinical and Translational Research center (CTRC) or in the UNC Hospitals Infusion Clinic. Subjects will be examined by a nephrologist, either their regular nephrologist or a nephrologist who is a member of the study team. Study-specific procedures for each visit are outlined below.

6.2. Subjects randomized to maintenance therapy: the treatment group

For Subjects randomized therapy, the first rituximab infusion (or the day an alternative therapy is started) will be their Visit 1. From that day, subject will be followed in a standard of care fashion, with visits scheduled every 8 to 12 weeks, as deemed necessary by study doctor. If a participant is not scheduled for a standard of care visit within an 8-12 week window, a remote visit will be done via phone or video to collect an interim medical history.

6.3. Schedule of visits post randomization:

6.3.1. WATCH group – no maintenance therapy-Study visit windows: +/- one week

Visit 1/ (= Week 0): The subject will have a physical exam including BVAS and CDA assessments. We will collect information on concomitant medications and AEs. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research purposes at the same time as standard of care labs, if ordered. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from B cell analysis in our study database.

Visits 2-5 (Weeks 4 - 16): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs in our study database.

At week 12, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

Visits 6 (Week 22): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research when the subject has blood drawn for routine labs, if applicable. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from the B cell analysis in our study database.

Visits 7-9 (Weeks 28 - 40): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs in our study database.

At week 34, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

Visit 10 (Week 46): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research when the subject has blood drawn for routine labs, if applicable. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from the B cell analysis in our study database.

Visits 11 - 13 (Weeks 52 - 64): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results of B cell analysis in our study database.

At Week 52, all subjects will also undergo a CDA assessment by the nephrologist.

At week 58, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

After Week 64, the visit schedule will change from every 4 weeks to every 6 weeks. Check in phone calls will continue to occur in between visits.

Visit 14 (Week 70): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research when the subject has blood drawn for routine labs (if applicable) . Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from the B cell analysis in our study database.

Visits 15 -17 (Weeks 76 -88): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs in our study database.

At week 82, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

Visit 18 (Week 94): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research when the subject has blood drawn for routine labs (if applicable) . Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from the B cell analysis in our study database.

Visits 19 - 20 (Weeks 100 - 106): The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs in our study database.

At week 106, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

At week 106, all subjects will undergo a CDA assessment by the nephrologist.

6.3.2. Treatment group

Visit 1/ (= Week 0): Subjects assigned to treatment groups will receive 500 mg IV rituximab (or start azathioprine or mycophenolate mofetil).

The subject will have a physical exam including BVAS and CDA assessments. We will collect information on concomitant medications and AEs. The subject will be asked to complete a quality of life questionnaire. We will collect 24 ml of blood for research purposes when the subject has blood drawn for routine labs. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs as well as results from B cell analysis in our study database.

Visits 2 to 13 The subject will have a routine clinical evaluation and a BVAS assessment. We will collect information on adverse events, concomitant medications, and medication compliance. Women of child-bearing potential will undergo a urine pregnancy test as per indicated clinical care. We will enter the results of routine labs in our study database.

Subjects in this treatment groups will receive 500 mg IV rituximab at week 22, week 46, week 70 and week 94 with a +/- 1 week window (or continue azathioprine or mycophenolate mofetil)..At those visits, prior to infusion, subjects will have 24 ml of blood drawn for research purposes, including analysis of B cell counts.

The visits will be between every 8 weeks to every 12 weeks, based upon the investigator assessment of how closely an individual subject needs to be followed while on maintenance therapy. The means that the subjects could have between 9 visits (if seen every 12 weeks) and 13 visits (f seen every 8 weeks) until the end of the study.

At week 106, all subjects will undergo a CDA assessment by the nephrologist.

Schedule of Visits and Events: WATCH group (no-maintenance therapy)

Visit	Physical Exam & Vitals	BVAS†	CDA‡	Concomitant Meds	QOL Q'naire	Adverse Events	Blood Collection for Research	Urine pregnancy test	Lab Data Collection
Enrollment	X	X		X	X		X	X	X
SOC visits until B Cell recovery	optional	optional		X				optional	X
Visit 1 (week 0)	X	X	X	X	X	X	X	X	X
14 days post-monthly visit call		Script		X					
Visit 2 (week 4)	X	X		X		X		X	X
Visit 3 (week 8)	X	X		X		X		X	X
Visit 4 (week 12)	X	X		X		X	X	X	X
Visit 5 (week 16)	X	X		X		X		X	X
Visit 6 (week 22)	X	X		X	X	X	X	X	X
Visit 7 (week 28)	X	X		X		X		X	X
Visit 8 (week 34)	X	X		X		X	X	X	X
Visit 9 (week 40)	X	X		X		X		X	X
Visit 10 (week 46)	X	X		X	X	X	X	X	X
Visit 11 (week 52)	X	X	X	X		X		X	X
Visit 12 (week 58)	X	X		X		X	X	X	X
Visit 13 (week 64)	X	X		X		X		X	X
Visit 14 (week 70)	X	X		X	X	X	X	X	X
Visit 15 (week 76)	X	X		X		X		X	X
Visit 16 (week 82)	X	X		X		X	X	X	X
Visit 17 (week 88)	X	X		X		X		X	X
Visit 18 (week 94)	X	X		X	X	X	X	X	X
Visit 19 (week 100)	X	X		X		X		X	X
Visit 20 (week 106)	X	X	X	X		X	X	X	X

† BVAS = Birmingham Vasculitis Assessment Score

‡ CDA = Combined Damage Assessment Index

X°

Schedule of Visits and Events: TREATMENT GROUP

Visit	Physical Exam & Vitals	BVAS†	CDA‡	Concomitant Meds	QOL Q'naire	Adverse Events	Blood Collection for Research	Urine pregnancy test	Lab Data Collection	Maintenance Therapy with Rituximab*
Enrollment	X	X		X	X		X[0]	X	X	
SOC until B Cell recovery	optional	optional		X				optional	X	
Visit 1/ (week 0)	X	X	X	X	X	X	**X***	X	X	**X***
Visit 2 (8 to 12 wks after V1)	X	X		X		X		X	X	
Visit 3 (8 to 12 wks after V2)	X	X		X	Xi	X		X	X	X*
Visit 4 (8 to 12 wks after V3)	X	X		X		X		X	X	
Visit 5 (8 to 12 wks after V4)	X	X		X	Xi	X	**X***	X	X	X*
Visit 6 (8 to 12 wks after V5)	X	X		X		X		X	X	
Visit 7 (8 to 12 wks after V6)	X	X		X	Xi	X	**X***	X	X	X*
Visit 8 (8 to 12 wks after V7)	X	X		X		X	[1]	X	X	
Visit 9 (8 to 12 wks after V8)*	X	X		X	Xi	X	**X***	X	X	X*
Visit 10 (8 to 12 wks after V9)*	X	X		X		X		X	X	
Visit 11 (8 to 12 wks after V10)*	X	X	X	X		X		X	X	
Visit 12 (8 to 12 wks after V11)*	X	X		X		X		X	X	
Visit 13 (8 to 12 wks after V12) *	X	X		X		X		X	X	

† BVAS = Birmingham Vasculitis Assessment Score

‡ CDA = Combined Damage Assessment Index

Maintenance therapy with rituximab (Rituxan) is administered at 500 mg IV every 6 months. The visit numbers when the infusion will happen are indicative . Infusion will be scheduled at week 0, week 22, week 46, week 70 and week 94 +/-1 week. Patients who are allergic or intolerant to rituximab or cannot access rituximab will receive maintenance therapy with azathioprine (Imuran) 1.5-2 mg/kg/day or mycophenolate mofetil (CellCept) 1000 mg twice daily. In the maintenance therapy group, B cell subsets will be measured prior to Rituximab infusion until Month 24. For subjects on maintenance therapy with azathioprine or mycophenolate mofetil, B-cell subsets will be measured at week 22, week 46, week 70 and week 94

Xi: Quality of Life questionnaire is administrered at infusion visit.

- The last study visit will take place when the 2 years post-randomization timepoint is reached.

7 Statistical Plan

Susan L. Hogan, PhD MPH and Yichun Hu, MS will be responsible for statistical computations for data analyses.

7.1 Sample Size Determination

Based on our ANCA cohort registry, we estimate being able to enroll 40 eligible patients over a period of 24 months. Based on our previous studies, we estimate that ~31 patients (78%) will recover ≥ 43%CD5+ B cells after induction therapy and will be randomized to maintenance vs NO maintenance immunosuppressive therapy arm. We anticipate 9 patients (22%) will fall in the "low" CD5+ B cell category and will receive maintenance therapy with rituximab, azathioprine or mycophenolate mofetil.

7.2 Statistical Methods

As a proof-of-concept trial, no statistical comparisons will be done, but summary statistics and graphical displays of the data will be observed for patterns and also used to calculate sample size estimates needed for statistical comparisons in a larger trial. Summary statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs).

For the descriptions of each analytic Aim below groups, will be defined as follows:

Cohort 1: Subjects in remission with CD19+CD5+ ≥ 43%

A) To discontinue maintenance immunosuppression (NO-Maintenance Therapy Group)
B) To continue on maintenance immunosuppression (Maintenance Therapy Group)

Cohort 2: Subjects in remission with CD19+CD5+ < 43%

B) To continue on maintenance immunosuppression (Maintenance Therapy Group)

Aim 1. Characterize and compare A and B in terms of the outcome variables, based on data from Cohort 1.

Aim 2. Characterize and compare A and B in terms of the outcome variables, based on Cohorts 1 and 2 combined.

Aim 3. Characterize and compare Cohort 1(B) and Cohort 2(B).

Aim 4. Characterize and compare Cohort 1(A) and Cohort 2(B).

Aim 5. Obtain point- and interval-estimates needed to plan a future confirmatory randomized clinical trial.

Time to first relapse – we will summarize the time (months) to relapse and plot Kaplan-Meier curves for time to FIRST relapse by each regimen and cohort, and calculate median time to relapse and a 24-month relapse-free survival rate for each group. We will calculate a univariate hazard ratio with 95% confidence interval using Cox regression models. No statistical analyses for comparisons will be done, but trends and relapse estimates by regimen and by cohort will be used for formulating a larger study. We are most interested in time to first relapse as that denotes a clinical end point for the study since it will require reinitiating induction therapy rather than maintenance or "no maintenance". However, we will continue to collect data on subjects with relapses for their full follow-up time to have some information on how these subjects respond to treatment and/or if they relapse again after being in this study.

Time to first positive ANCA test (among those negative at randomization) – The percent who develop a positive ANCA test, and timing to a positive ANCA test will be summarized, with plots of time to this event using Kaplan-Meier curves generated. No statistical analyses for comparisons will be done, but trends and estimates by regimen and by cohort will be used to inform a larger study.

Frequency (number) and severity (by BVAS) of relapse – Among those who relapse, we will evaluate which organs are impacted by disease relapse (using BVAS subsections) and the severity of the relapse

(summarized by the BVAS score). This will be done by regimen and by cohort. Zero in any organ sub-section shows no disease activity in that organ. The total score range for a BVAS is 0 to 64. No statistical analyses are planned, but this will provide information for potential patters of relapse in specific organs as well as information on the severity of relapses by group.

Occurrence of any infection – all infections will be counted and described by regimen and by cohort.

Frequency/severity/etiology of infections – recurrent infections, severity of infections, with those requiring hospitalization and/or intravenous antibiotics deemed as serious–with etiology of each infection listed. Etiologies will be listed as reported and may include a combination of location (urinary tract, upper respiratory, lung) and type of pathogen (bacterial, viral, fungal or parasitic). All infection metrics (recurrent, severity and type) be described and tallied within each regimen and cohort, but no statistical comparisons will be done. This information is necessary to understand the expected infectious adverse events that can be expected in a larger study.

Frequency and severity of any adverse advent (AEs and SAEs) – These will be catalogued as above for infections – including type of event, relation to therapy/discontinuation of therapy, and outcome of adverse event.

Time to B-cell normalization (that is, % IL-10 Secreting > 45% or % CD5+ B Cells Response > 43%) – the number who normalize will be evaluated; time to normalization will be observed in Kaplan-Meier plots by each regimen and cohort, but no statistical tests will be done to compare groups. These measures will guide the optimal times for follow-up and monitoring in a larger study.

Note about determination of relapse: In cases where the assessment of relapse performed by Dr. Rivadeneira differs from that of the treating physician's assessment, the assessment used for final data analysis will be Dr. Rivadeneira's.

Missing Data: Missing values will not be imputed. For those who drop out of the study prior to reaching an outcome, they will contribute the time they were followed. For those who miss visits and do not have laboratory values assessed, we will use the next available to determine their time to normalization of a value. If patients report infections, we may not have details on the location or type, but will report the counts with and without patient-only reported infections (verification of infections by outside providers or hospitals will be included in the study counts and not be deemed as reported by the patient only). We anticipate minimal missing data as nearly all measures will be obtained in the setting of routine clinical practice. If patients are seen elsewhere, we will need to get outside medical records. Reasons for missing data and protocol violations will be documented in the database.

7.3 Subject Population(s) for Analysis

All study subjects enrolled will be included in our analysis.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency
- Related or possibly related to participation in the research
- Serious (as defined below)

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Grading the Severity of Adverse Events (Common Terminology Criteria for Adverse Events v.4.0[CTCAE])

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*. An infection requiring oral antibiotics and resulting in interruption of school or work ≤1 day, is considered a Grade 2 infection.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living**. An infection requiring hospitalization or IV antibiotics or resulting in interruption of school or work > 1 day will be considered a Grade 3 infection
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

For the purpose of this trial, any of the signs, symptoms, or conditions listed under warnings and adverse reactions for rituximab, azathioprine and mycophenolate mofetil under section 1.2 will be considered expected adverse events:

Adverse Event Reporting Period

The study period during which adverse events will be reported will be defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the FDA of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The FDA will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality will be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery will be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery will be reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedure results will be recorded in the source document, though grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

All adverse events will be reviewed and recorded in “real time” and reviewed systematically every month by the PI. Adverse events are defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, disease, or abnormal laboratory finding temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

Serious Adverse Events (SAE) will be reported immediately within 1 business days to the UNC IRB, and within 5 business days to the FDA according to the requirements of the IND. Reporting will be done electronically to the UNC IRB (as per current standard operating procedure) and by Fax to both institutions.

For reportable deaths, the initial submission to the UNC IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:

The following events will also be reported to the UNC IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug.
- Any adverse event that would require modifications to the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency

- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Incarceration of a subject when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation or deviation.

8.3.1 Notifying the FDA

The PI will report certain study events (IND safety reports) in an expedited fashion to the FDA. These written notifications of adverse events are referred to as. The following describes the safety reporting requirements which will be followed by timeline for reporting and associated type of event:

- ***Within 7 calendar days***

  Any study event that is:

  – associated with the use of the study drug

  – unexpected,

  – fatal or life-threatening, and

- ***Within 15 calendar days***

  Any study event that is:

  – associated with the use of the study drug,

  – unexpected, and

  – serious, but not fatal or life-threatening

  -or-

  – a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

  – suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

The PI will also identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Adverse events will be submitted on our SAE form (see Appendix D) or in a narrative format, along with FDA form 1571. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section.

8.4 Stopping Rules

Trial Termination: It is anticipated that some of the patients will have a relapse even among those treated with maintenance immunosuppression. In a recent large randomized controlled trial of maintenance therapy with rituximab vs azathioprine, 5% of patients in the rituximab-treated group and 29% of those in the azathioprine-treated group had a major relapse over 28 months of follow up (Guillevin L et al *N Engl J Med 2014;371:1771-80.)*. Major relapses were defined as involving a major organ or life threatening (e.g. alveolar hemorrhage, glomerulonephritis, mononeuritis with new motor deficits). In addition, minor relapses (e.g. recurrence of epistaxis, arthralgias, or skin rash) occurred with greater frequency (e.g. in the RCT trial of maintenance therapy with rituximab vs azathioprine, minor relapses occurred in 11% vs 16% of patients respectively).

In order to minimize bias in the assessment of the primary endpoint of relapse, this relapse assessment will be done by a physician serving as a reviewer blinded to the patients' identity and treatment arm. Dr. Rivadeneira, Associate Professor of Medicine, Associate Division Chief, Division of Rheumatology, Allergy, and Immunology at UNC will serve as the blinded reviewer for this study. Dr. Rivadeneira has vast experience and expertise in ANCA vasculitis. Dr. Rivadeneira will NOT be involved in the care of patients enrolled in this study. Every 3 months, Dr. Rivadeneira will review all of the available clinical assessments for relapse adjudications based on the BVAS scores, clinical history, review of systems, physical examination and laboratory data. A report form will be generated to provide him with this information while being blinded to the treatment arm (medication list will be omitted). Patients will be treated according to the treating-physican's assessment in the interval between these blinded reviews. Dr. Rivadeneira's assessment will not be used to guide therapy. For the purpose of data analysis, in cases where the assessment of relapse done by Dr. Rivadeneira differs from the treating physician's assessment, the assessment used for final data analysis will be the blinded reviewer (Dr. Rivadeneira).

Given the small number of patients in each treatment group in our proposed proof of concept trial (~15 patient per group), it is difficult to decide a priori of a number of relapses in the No-maintenance therapy group that would prompt termination of the trial. We propose prompt consideration of early termination of the trial if the following criteria are met at any point over the course of the trial (provided a sufficient number of patients are accrued and randomized):

1) ≥ 50% major relapse rate in the NO-maintenance therapy group, AND

2) ≥ 40% major severe relapse rate over the maintenance therapy (control) group. Major relapse is defined as involving a major organ or life threatening (e.g. alveolar hemorrhage, glomerulonephritis, mononeuritis with new motor deficits).

The DSMB will be contacted for a review of the study outcomes whenever 2 new relapses have occurred in the NO-maintenance therapy (surveillance) group.

The "≥40% major severe relapse rate over the Maintenance Therapy Group" criterion stems from the small number of patients anticipated in each of the randomized groups (about 15 per group) and for the recognized potential relapse rate in the control (maintenance immunotherapy) group (in the MAINRITSAN trial, the major relapse rates were 5% and 29% over 28 months for the rituximab and azathioprine groups respectively) *(Guillevin L et al* N Engl J Med 2014;371:1771-80.).

During the conduct of the trial, and before all the patients are accrued, a threshold of 50% relapse rate may be attained with a very small number of events (1-2). The additional ≥40% over the Maintenance Therapy criterion is meant to verify that the study is not terminated prematurely by a chance event.

Conversely, we propose the following criterion to prompt consideration of early termination of the trial for toxicity if there is a ≥ 40% increase in Grade 3 severe serious adverse event rate in the maintenance therapy (control) group compared to the NO-maintenance therapy group.

Treatment Stopping Rules:

We do not have criteria for withdrawing individual subjects from the study.

If a subject in either treatment group (maintenance therapy or no maintenance therapy group) relapses, s/he will receive treatment at the discretion of the nephrologist managing his/her care. That will end the interventional phase of the subject's participation. However, we will continue to follow the subject (collect information and blood) for the full 24 months of post randomization follow up.

If a subject in the maintenance therapy group experiences a non-infectious adverse event attributable to the maintenance medication (e.g. allergic reaction) s/he is receiving (rituximab, azathioprine, MMF), this medication will be discontinued and the patient will be switched to another immunosuppressive medication per the patient's treating nephrologist.

Infectious adverse events are common in all forms of immunosuppressive therapy. Severe (Grade 3) infectious adverse events will result in temporary interruption of azathioprine or MMF therapy, or postponement of rituximab therapy, until the infection is fully treated. Grade 4 infectious adverse events will lead to the permanent discontinuation of maintenance immunosuppressive therapy. Grade 3 infectious adverse events may also lead to permanent discontinuation of maintenance immunosuppressive therapy based on the judgement of the treating physician.

If a subject in the maintenance therapy group wishes or needs to discontinue therapy, therapy will be stopped. That will end the interventional phase of the subject's participation. However, we will continue to follow the subject (collect information and blood) for the full 24 months of post randomization follow up.

8.5 Safety Monitoring

8.5.1 Internal Data and Safety Monitoring Board or DSMB

We will use the UNC North Carolina Translational & Clinical Sciences Institute (NC TraCS) DSMB.

The Charter of the NC TraCS DSMB is included in Appendix A, detailing the members, protocol review and monitoring process. The protocol is submitted for review by the DSMB. Changes (if any) to the DSMB monitoring plan will be developed in accordance with DSMB recommendations. We request that DSMB review of the study be started when 8 patients have been randomized to NO maintenance vs maintenance immunosuppression, and every 6 months thereafter. We also request that the DSMB review the frequency and severity of adverse events and relapses in the NO maintenance compared to the maintenance immunosuppression groups.

The NC TraCS DSMB monitors studies for safety and/or efficacy. Source document data monitoring for accuracy and completeness will be done by a UNC Research Coordinator NOT involved in this study, who will review CRFs and source documentation on a regular basis to determine proper adherence to the protocol with collection of all relevant documentation to support the study.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Patients will be assigned unique study IDs which will be used on hard copy documents for identification purposes in lieu of personal identifiers. Personal identifiers will be redacted on paper documents which print with identifiers

(e.g. medical records). Study binders will be stored in a locked cabinet in UNC Kidney Center office space which is locked during off hours. These documents will be kept in secure long-term storage for the period of time required by institutional and FDA regulations and will then be shredded and disposed of securely.

We will create a screening log in Excel. This log will be password protected and maintained on a secure UNC Kidney Center server. Only authorized study personnel will have access to this file. We will collect only the minimum amount of information necessary for screening purposes. This will include name and medical record number so that we can keep track of which patients have been screened and evaluate patient eligibility for the study on an ongoing basis if needed (e.g. track treatment and disease status). This log will be deleted once enrollment is closed.

We will create a REDCap database which will store demographic, clinical, and research data. This database will be password protected and will reside on a secure UNC Kidney Center server. Only authorized study personnel will have access to this file. We will collect data on demographics, routine labs, BVAS and CDA scores, B cell counts, AEs, concomitant medications, medication compliance, and quality of life. This file will be deleted once data analysis has been completed.

Biological samples will be labeled with the subject's study ID and a unique bar code. These samples will be tracked in the IRB-approved GDCN database. Samples will be destroyed once the study is completed, including data analysis.

9.2 Source Documents

Source data will be drawn from the following source documents: records contained in the UNC electronic record, including clinic notes, inpatient notes, laboratory results, pathology reports, operative notes, radiology reports, procedure notes and documents from outside sources which have been scanned into the electronic record. Source documents will also include assessment forms completed by study physicians (CDA and BVAS), case report forms, and questionnaires completed by the subjects.

9.3 Case Report Forms (as applicable)

Case report forms will be developed by the study coordinator and include forms for collecting information on demographics, medical history, concurrent meds., AEs, protocol deviations, medication compliance, laboratory results, disease status, vital signs and quality of life. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, we will write “N/D”. If the item is not applicable to the individual case, we will write “N/A”. All entries will be printed legibly in black ink. If any entry error has been made we will draw a single straight line through the incorrect entry and enter the correct data above it. All such changes will be initialed and dated. We will not white our or erase errors. For clarification of illegible or uncertain entries, we will print the clarification above the item, then initial and date it.

9.4 Records Retention

We will retain study essential documents for 2 years after the completion of the study.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will follow the monitoring plan established by the UNC TraCS DSMB.

10.2 Auditing and Inspecting

We will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Ethical Considerations

This study is a proof of concept study testing the hypothesis that patients in complete remission after induction therapy, and with recovery of B cells with a normalization of CD5+ B cells may avoid exposure to maintenance immunosuppression. The randomization in this study may be justified by the following considerations:

1) There is clinical precedence to following patients treated with induction therapy with rituximab and corticosteroids without additional maintenance therapy. In the landmark study of induction therapy with corticosteroids in combination with rituximab vs cyclophosphamide x 3 months followed by azathioprine maintenance therapy, patients assigned to the rituximab group did NOT receive any additional maintenance therapy after the initial four weekly doses of rituximab. (Stone JH 2010).

2) In this randomized controlled trial, induction therapy with rituximab and NO maintenance therapy was not associated with a statistically significantly different rate of relapse, and a statistically significantly LOWER rate of adverse events. While the latter results cannot be directly attributable to the avoidance of maintenance immunotherapy, it raises the possibility that such avoidance may in fact be associated with a decreased risk of infectious complications.

3) Patients will be followed carefully with frequent clinic visits to detect any early signs of relapse. Any sign of relapse will result in exiting the patient from the investigational part of the study and instituting immunotherapy at the decision of the treating nephrologist.

This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See **Appendix B** for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

National Institutes of Health

12.2 Conflict of Interest

This study is supported by an NIDDK grant (P01-DK058335-16), with no additional support. There is not external support from industry. As such, we anticipate no conflict of interest from any investigator. All study personnel have completed the UNC conflict of interest attestation.

13 Publication Plan

This study is conducted as a single center study at the UNC Kidney Center, under a grant from the NIDDK. The conduct of the trial, review of the data and its analysis will be performed by the co-investigators and research staff. No approval requirements from parties external to the research team are anticipated. Access to the publication and data will be in accordance to the general policies of the NIH and University of North Carolina.

We will plan to publish descriptive information and outcomes from the study. This will be done to make results available to the research community with the intent of informing but also with the potential for collaboration with other sites who see these patients for participation in a future trial. The publication may be in the form of a short report aimed at describing the ability of enrolling patients into this type of study and to show where data for sample size estimates will be drawn from.

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14 Appendices

Appendix A: DSMB charter

North Carolina Translational and Clinical Sciences (TraCS) Institute

Data Safety Monitoring Board (DSMB) Charter

Revised 10/19/2017

Table of Contents

Abbreviations

AE	Adverse event
DSMB	Data and Safety Monitoring Board, NC TraCS Institute
DSMC	Lineberger Data and Safety Monitoring Committee, PRC
CTRC	Clinical and Translational Research Center
IRB	UNC Biomedical Institutional Review Board
NIH	National Institutes of Health
PI	Principal Investigator
PRC	UNC Lineberger Oncology Protocol Review Committee
TraCS	North Carolina Translational and Clinical Sciences Institute
UNC	University of North Carolina at Chapel Hill

Introduction

The North Carolina Translational and Clinical Sciences (TraCS) Institute is committed to the safety of patients participating in clinical trials at our institution. In addition, it is committed to data accuracy and protocol compliance. The NC TraCS Institute has established an institutional plan to provide data safety and monitoring for selected clinical trials conducted at UNC. This plan is designed to comply with policies and guidelines regarding data and safety monitoring from the National Institutes of Health (http://grants.nih.gov/grants/guide/notice-files/not98-084.html; http://nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).

This charter is for the Data Safety and Monitoring Board (DSMB) of the North Carolina TraCS Institute. The charter contains the following:

- A description of the composition and organization of the DSMB
- Details the roles and responsibilities of DSMB members
- Outlines the responsibilities of the Principal Investigators and Sponsors
- Lists important contact persons

Organization

Overview

The DSMB functions as a committee within the NC TraCS Institute. The charge to the DSMB is review clinical trials to assure patient safety both by evaluating adverse events (AEs) and interim analyses of both safety and efficacy.

Committee Structure

The DSMB Chair (currently Dr. Ross Simpson) has the overall responsibility for the chairing the DSMB committee and reporting its findings to the UNC Biomedical IRB. The Committee will be under the direct supervision of the NC TraCS Institute Director or designated representative. The Committee will consist of a chair, an ethicist, an epidemiologist, a biostatistician, and one or more clinical researchers. Committee members will serve for 3-year terms, but may be reappointed. Members will be appointed to the Committee by the Chair, Director or designated representative. A member of the DSMB can be removed due to poor attendance, inadequate demonstration of effort, unprofessional conduct and /or failure to act in accordance with the objectives of the DSMB. A list of current DSMB members can be found in Appendix 1.

PROCESS

Eligibility

A clinical trial is defined as “a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavior interventions; these may include drugs, treatments, devices, or behavior or nutritional strategies.” Studies that include nutritional, behavioral, and psychosocial interventions are considered to be clinical trials. Studies evaluating diagnostics (imaging, etc.) in which findings alter the patient’s clinical care are also considered to be clinical trials. Observational studies, epidemiologic studies, studies of diagnostics that do not affect patient care, and studies that do not test interventions are not considered to be clinical trials.

DSMB Functions and Activities

The DSMB is responsible for reviewing data from clinical trials approved by the UNC Biomedical IRB. Investigators with commercially or governmentally sponsored trials will normally work with their sponsor’s DSMB.

The DSMB will review data from the following types of trials, when review is deemed necessary by the Biomedical IRB or requested by the Principal Investigator (PI), in order to ensure the safety of participating subjects.

- Phase I, I/II, II, and II/III trials when such review is deemed necessary by the UNC Biomedical Institutional Review Board and the Principal Investigator.
- Phase III clinical trials (single site trials where the PI is a UNC faculty member and for which UNC is the sponsor)
- Phase IV clinical trials (single site trials where the PI is a UNC faculty member and for which UNC is the sponsor)
- Select multicenter clinical trials in which UNC is the coordinating center or the PI of the study is a UNC faculty member IF the DSMB determines that it has adequate resources to conduct the monitoring required of the study.

The DSMB will meet at least every other month and has the following responsibilities.

- Assessing risk and complexity of clinical trials submitted for review
- Determining the appropriate level of data and safety monitoring
- Reviewing serious adverse events (AEs) reports when requested.
- Reviewing yearly data and safety monitoring reports when requested. Recommending appropriate actions (closure, increased monitoring, etc.) to the Principal Investigator, UNC Biomedical IRB, and the Director or designated representative.
- Communicating its finding with the Biomedical IRB
- Preparing minutes for all meetings
- Preparing an annual summary of activity for review by the Director, NC TraCS Institute
- Review of the monthly reports of the UNC Lineberger Oncology Protocol Review Committee (PRC) -Data and Safety Monitoring Subcommittee (DSMS)
- Assessing ethical and scientific soundness of trials reviewed

DSMB-Investigator Communications

The DSMB will make available to investigators the following:

- An Annual Data Reporting form for annual reporting of all AEs
- A Data Safety Monitoring Plan template

Principal Investigators shall make available to the DSMB the following information:

- A copy of the approval letter from the UNC Biomedical Institutional Review Board
- A Data Safety Monitoring Plan
- All adverse event reports using the most current UNC Biomedical Institutional Review Board form
- An annual summary of all AEs

Relation to Biomedical Institutional Review Board and Lineberger Oncology Protocol Review Committee

The DSMB will report its findings and make recommendations to the UNC Biomedical IRB. For research conducted by the Lineberger Cancer Center, the DSMB will report its findings and make recommendations to the UNC Lineberger Oncology Protocol Review Committee (PRC). Trials required to have an independent data and safety monitoring board as defined in this charter are expected to use the NC TraCS Institute DSMB instead of establishing their own independent board, unless outside expertise not available on the DSMB is necessary to adequately monitor the trial.

Notice of a recommendation of early closure or suspension will be reported directly to the Biomedical IRB and the Director or designated representative. As appropriate, such recommendations will be reported to the Director of the Lineberger Cancer Center and the Director of the Clinical Translational Research Center. The Chair of the DSMB in conjunction with the Chair of the Biomedical IRB is responsible for seeing that these trials are closed to accrual.

Guidelines for Members

In order for the DSMB to fulfill its responsibilities, the member will observe the following guidelines:

- Members are free of apparent conflicts of interest involving financial, scientific, or regulatory matters. In case of any question of conflict of interest, standards used by NIH in determining conflict of interest for advisory committee members and investigators shall apply.
- Members should assess trial objectives and design in an unbiased way.
- Members are guided both by pre-specified study performance criteria, such as early stopping rules, and also by a masked and, if necessary, unmasked review of all data prior to making decisions
- The DSMB members will review data and pertinent procedures in order to be confident that the data on which the decisions are based are accurate and complete.
- All decisions of the DSMB shall be independent

PROTOCOL REVIEW AND DATA MONITORING

Monitoring and Reporting Requirements

In collaboration with the Principal Investigator and study biostatistician, the DSMB will set data monitoring and reporting requirements before study enrollment begins. Members will review the interim analysis plan to ensure the analyses planned will provide necessary information for DSMB decisions. Members will participate in specification and review of all tables and specifications for data that they will review in accordance with timelines established by agreement with the Principal Investigator.

The DSMB will have face-to-face meeting(s) to review and discuss results of interim analysis. The DSMB may also have face-to-face meeting(s) as prompted by unplanned interim analyses deemed necessary because of safety concerns. The DSMB staff or chair will prepare minutes of each meeting within ten (10) working days of each meeting. These minutes will be circulated and approved at the next regularly scheduled meeting of the DSMB.

The Principal Investigator and study biostatistician will work with the DSMB for appropriate preparation of reports to be viewed at DSMB meetings and resolution of questions arising during data analysis. If requested by the DSMB, the Principal Investigator will turn over to the chairperson of the DSMB evidence of validation of all computer programs used to generate reports and analyses for each DSMB meeting. The documents will be made part of the minutes of each meeting. All formal reports will be circulated to the DSMB members no later than one week prior to each DSMB meeting.

Data Review by the DSMB

DSMB meetings will consist of an open and a closed session. The open session will provide a forum for exchange of information among DSMB members, Principal Investigator, and study biostatistician. During the open session, the Principal Investigator may present a brief summary report of the study progress, including enrollment rates, data collection, and data quality. There will be an opportunity for the Principal Investigator to ask advice from the DSMB on any matter concerning conduct of the trial.

Only members of the DSMB will attend the closed session. During this session, the DSMB will address issues regarding the following: 1) safety concerns, 2) efficacy concerns, 3) termination of the trial due to pre-specified stopping criteria, and 4) ethical concerns. The DSMB will be furnished with relevant information by the Principal Investigator to make these decisions. During this session the DSMB members may ask the Principal Investigator to provide them with data that is partially unmasked (i.e., treatment A or treatment B without revealing what treatment A and B represent) or completely unmasked (i.e., identify treatment group).

In addition to the open and closed sessions, the voting members of the DSMB may meet in an executive session at their discretion. The DSMB will:

- Review the protocol and any protocol amendments
- Review the interim analysis monitoring plan, make recommendations, and give approval
- Review interim analysis reports and meet as a group
- Communicate recommendations in writing to the Principal Investigator

If there are any concerns about reviewed material (such as safety, efficacy, ethics, and stopping rules), the DSMB will take appropriate action. This may involve a request for additional information, or a request for an early, unscheduled meeting of the DSMB with the Principal Investigator and study biostatistician. At each meeting that includes review of interim data, the DSMB will recommend one of the following actions to the Principal Investigator, Biomedical IRB, and when appropriate the NC TraCS Institute Director or designated representative.

- Continue the study according to the protocol.
- Modify the study protocol. Modifications may include such items as changes in the inclusion/exclusion criteria, nature and frequency of safety monitoring, study procedures, study drug/intervention dosing, consent form changes, subject re-notification, and any other changes deemed necessary.
- Discontinue one or more study arms.
- Discontinue the study.

The DSMB may request additional data, analyses, or meetings to address specific concerns. The DSMB may hold additional meetings without knowledge of the sponsor or Principal Investigator.

Release of DSMB Recommendations

The DSMB will refrain from revealing to the sponsor, Principal Investigator, or any other party information that would lead to compromising the integrity of the trial unless such a release is required to protect subject safety. In particular, the following guidelines will be followed with respect to the dissemination of the DSMB interim analysis results.

- Individual patient treatment assignments will not be revealed
- Individual center results will not be revealed
- The magnitude of treatment differences in efficacy will not be revealed
- Study results will not be communicated to investigators
- The DSMB will not make any public disclosures of its discussions and decisions
- The DSMB will complete a brief report documenting decisions and rationale behind its decisions. The report will be conveyed confidentially to the Principal Investigator and sponsor, who in turn, will forward it to appropriate regulatory agencies. A copy of the report will also be made available to the UNC Biomedical Institutional Review Board, in form that does not contain information that could compromise the integrity of the clinical trial.
- When appropriate a copy of the report will also be made available to the Director of the Lineberger Cancer Center and/or the Director of the Clinical Translational Research Center.
- All DSMB decisions will be deemed advisory to the Principal Investigator, UNC Biomedical Institutional Review Board, and the Director, NC TraCS Institute.

Appendix 1: NC TraCS Institute DSMB Members, Year 2016 - 2018

Member	Department/School	Email
Ross J. Simpson, Jr., MD, PhD (chair)	Medicine	rsimpson@med.unc.edu
David Weber, MD, MPH	Medicine	dweber@unch.unc.edu
David Couper, PhD	Biostatistics	david_couper@unc.edu
Marie Rape, RN, BSN	NC TraCS Institute	
Elizabeth Geller, MD	Obstetrics/Gynecology	elizabeth_geller@med.unc.edu
Samantha Meltzer-Brody, MD, MPH	Psychiatry	samantha_meltzer-brody@med.unc.edu
Lori Carter-Edwards, PhD	Public Health	lori_carter-edwards@unc.edu
William A. Fischer II, MD	Pulmonary and Critical Care Medicine	william_fischer@med.unc.edu

Appendix B: Consent form

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: October 22, 2024

IRB Study # 18-2015
Title of Study: Tailoring Maintenance Therapy to CD5+ Regulatory B Cell Recovery in ANCA vasculitis
Principal Investigator: Vimal K. Derebail
Principal Investigator Department: Medicine-Nephrology
Principal Investigator Phone number: (919) 966-2561
Principal Investigator Email Address: vimal_derebail@med.unc.edu
Co-Investigators: Ronald Falk, Jerry Hladik, Donna Bunch, John Schmitz, Shannon Mahoney, Koyal Jain, Manish Saha, Dhruti Chen

Funding Source and/or Sponsor: National Institutes of Health (NIH)
Study Contact Telephone Number: (919) 966-2561

Concise Summary

This is a study for adult patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis who are in remission after initial treatment. The purpose of this research study is to learn if a special blood test can help us identify which patients with ANCA vasculitis could be monitored without additional immunosuppressive maintenance treatment. This study is NOT testing new medications. Any treatment will use the same medications that are currently routinely used for maintenance treatment in ANCA vasculitis.

The study will last 2 years. Your initial treatment has eliminated certain immune cells (called “B lymphocytes” or “B cells”) from your blood. When we can detect the B cells again in your blood, it is time to decide if you need maintenance therapy. This is the time you can start in the study. At that stage, we believe that the number of a special type of B cells (called CD5+) can give us an indication of your risk of having a relapse of ANCA vasculitis in the future. If the number of CD5+ B cells is near normal, we believe that the risk of relapse is significantly lower than if that number is still abnormally low.

Therefore, if your CD5+ B cells are low, you will receive maintenance treatment as is usually done, using the same medications you would receive if you were not participating in this trial.

If your CD5+ B cells are near normal, you will be selected by chance (like flipping a coin) to either receive the same maintenance treatment or be monitored in clinic without additional maintenance treatment.

From that point forward, you will have clinic visits scheduled depending upon which study group you are assigned, for a total of 24 months or 2 years.

Potential benefit: Research is designed to benefit society by gaining new knowledge. There is little chance you will benefit from being in this research study.

Potential risk: If we think that you are at risk for relapse, you will receive maintenance therapy. If we think you are in the “low-risk-of-relapse” group, you will be randomized to receive or not receive maintenance therapy.

Being in the "low-risk-of-relapse" group does not mean you will never have a relapse. It is possible that being placed into the group receiving no maintenance therapy will put you at risk for relapsing or for relapsing sooner than if you had received maintenance therapy. However, you will be monitored closely throughout the study period so that if you do have a relapse of disease, we will be able to treat it promptly.

What are some general things you should know about research studies?

You are being asked to take part in a research study. To join the study is voluntary. You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

Patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis are routinely treated with medications that decrease their immune system function ("immunosuppression"). The treatments last several months and are divided in two phases: an "induction" phase is the initial phase aimed at stopping the inflammation, and a "maintenance" phase aimed at decreasing the risk of relapse. The risk of relapse varies considerably between patients, and we believe that some patients have a relatively low risk of relapse and may not need continued maintenance immunosuppression.

The purpose of this research study is to learn if a special blood test can help us identify some patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis who are in remission after initial treatment could be monitored without additional immunosuppressive maintenance treatment. By collecting health information and laboratory samples, our goal is to learn more about this disease and find better ways to tailor treatment of ANCA vasculitis to an individual patient's needs. New knowledge will be shared with researchers and the public.

You are being asked to be in the research study because you are between 18-85 years old and have been diagnosed with ANCA glomerulonephritis or vasculitis, you have been treated for 3 months or more and you have not had any symptoms of vasculitis for at least 1 month.

Are there any reasons you should not be in this study?

You should not be in this study if any of the following are true:

1) You do not wish to participate in this research study

2) You have already been sick with ANCA vasculitis 3 times or more (had 2 relapses or more)

3) You are participating in another clinical trial that determines your treatment of ANCA vasculitis

4) You have ANCA vasculitis that has been caused by a drug you were taking

5) You have active tuberculosis, human immunodeficiency virus (HIV, the virus that causes AIDS), hepatitis C virus or hepatitis B virus infections, or another active infection requiring IV antibiotics within 3 months of starting this research study.

6) You are a woman of child-bearing age and are unwilling or unable to use birth control

7) You are unable to come your scheduled appointments

How many people will take part in this study?

There will be approximately 40 people in this research study.

How long will your part in this study last?

Your participation in this research study will last 2 years. The treatment you have received for ANCA vasculitis decreases the function of your immune system. If you are enrolled in this study, it means that you have already completed the initial (induction) phase of treatment for ANCA vasculitis, and your disease is currently not active. The treatment you have received had eliminated certain immune cells (called “B lymphocytes” or “B cells”) from your blood but now, those B cells have returned.

At that stage, we believe that the number of a special type of B cells (called CD5+) can give us an indication of your risk of having a relapse of ANCA vasculitis in the future. If the number of CD5+ B cells is near normal, we believe that the risk of relapse is significantly lower than if that number is still abnormally low.

When the B cells are detectable in the blood, if your CD5+ B cells are low, you will receive maintenance treatment as is usually done, using the same medications you would receive if you were not participating in this trial. If your CD5+ B cells are near normal, you will be selected by chance (like flipping a coin) to either receive the same maintenance treatment or be monitored in clinic without additional maintenance treatment.

If you are in the group on maintenance therapy, you will have a clinic visit with a study physician every 8- 12 weeks, for a maximum of 24 months.

If you are randomized to NOT receive maintenance therapy and to be watched closely, you will be seen for clinic visits every 4 weeks for the first four months, then every 6 weeks for a total of 24 months of follow-up. You will also receive a phone call by a research coordinator about 2-3 weeks after every clinic visit to ask about any symptoms of infection or relapse.

This study is NOT testing new medications. Any treatment will use the same medications that are currently routinely used for maintenance treatment in ANCA vasculitis. This study is testing whether some patients whose CD5+ B cells return to near normal levels can be followed without receiving additional maintenance treatment.

You should be aware that the use of CD5+ B cells to guide treatment decisions is NOT currently approved by the FDA. These tests are to only be used in the *investigational* setting as noted below.

CAUTION – Use of an Investigational device. Limited by United States law to investigational use. Enumeration of B-cells for guiding management of ANCA vasculitis or other disease conditions has yet to be validated in clinical trials and should not be utilized to guide clinical therapy outside of a regulated, investigational study. This test was developed, and its performance characteristics determined by the McLendon Clinical Flow Cytometry Laboratory. The Flow Laboratory is CLIA certified and CAP accredited to perform high complexity testing.

What will happen if you take part in the study?

Enrollment visit

This visit can occur the day of your scheduled appointment in the UNC Kidney and Hypertension clinic. A member of the research team will tell you why we do this study, will explain how many study visits would happen and what will be done at each visit, and will see if you want to participate. You will be given several documents (called consent forms) to review. You will be given time to ask questions. You can read these at your visit or decide to take them home to read and discuss with your loved ones. If you choose to participate in the study, you will sign the consent forms. You will be given signed copies for your records. This process should take 20-30 minutes extra during your regular scheduled appointment.

If you decide to wait to consent, we can schedule another visit (Screening visit) where you can ask any further questions before you sign the consent. We would like this visit to be scheduled within 2 weeks of your regular visit so that we can make sure you are not in relapse before you consent.

Screening (Visit 0)

This visit can be done during your regular scheduled visit or at a future date. During this visit, you will have a physical examination by the doctor. The research coordinator will collect information about you, your medications and your previous medical history. We will need to draw an extra 24 mL of blood (a little less than 2 tablespoons) along with your standard of care blood tests.

If this visit takes place within 2 weeks of your regular Nephrology visit, we will only need to draw the 24 mL of blood for the research study and you will not need to repeat the physical exam at that visit.

We will measure the level of the special CD5+ B cells. If these are low, you will be started on maintenance treatment with rituximab. If you cannot take rituximab (500 mg by vein every 6 months), you will receive treatment with either azathioprine (Imuran) or mycophenolate mofetil (Cellcept) by mouth every day. These three medications are currently routinely used for maintenance treatment of ANCA vasculitis. The choice of which one will be prescribed to you will depend on how you tolerated them in the past, or whether your insurance company will cover the cost.

If your CD5+ B cells are near normal, you will be randomized, which means selected by chance (like flipping a coin) to either be in **the Maintenance Therapy group** where you will receive a maintenance treatment or to be in the **WATCH group** in which you will be monitored without maintenance treatment.. If you are randomized to receive maintenance treatment, you will receive rituximab (500 mg by vein every 6 months). If you cannot take

rituximab, you will receive treatment with either azathioprine (Imuran) or mycophenolate mofetil (Cellcept) by mouth every day.

Test Information: After consent, we will collect blood and urine samples from you at all study visits.

Total Amount of blood drawn: You will have between 10 to 16 tablespoons of blood (144 to 240 mL) taken for research during the study.

For the Maintenance Therapy Group

The maintenance treatment will start as soon as possible after we know that you are in the Maintenance Therapy group.

If you can receive rituximab: An appointment to have the rituximab infusion will be scheduled to be given at the UNC Infusion clinic. This medication is given by vein through an IV catheter. The infusion will take between four and six hours. At the time of each infusion you will be given a dose of "steroid" by vein and an antihistamine before the rituximab infusion to reduce the risk of allergic reaction. This is according to the standard protocol for the use of rituximab. This will minimize infusion reactions.

If you cannot tolerate Rituximab or if you cannot access rituximab (for example if your insurance does not agree to pay for it), your doctor will prescribe another maintenance drug: azathioprine or mycophenolate mofetil. Azathioprine and mycophenolate mofetil are oral drugs that you must take every daily.

You will have a research study visit at your infusion or at the start of the other medication. This visit will include:

- a physical exam
- vital signs (blood pressure, weight, temperature, respiration rate)
- you will give a urine sample
- you will have a blood drawn, for your care and sometimes for research (see the schedule of visits table for more info- each research blood draw is 24 mL = a bit less than 2 tablespoons)
- if you are a woman who could become pregnant, we will do a urine pregnancy test
- the doctor will review your medications and how you feel
- about every 4 months you will fill out a questionnaire about your quality of life

After the infusion or start of medication, the Maintenance Therapy group will have clinic visits for the study every 8-12 weeks for the doctor to make sure you are well and watch for relapse symptoms and the return of the B cells. The actual schedule will vary and depend upon your health and the doctor's guidance. These visits will be very similar to the visit mentioned above. **You will receive further Maintenance medication for relapse symptoms or the return of the B cells.**

In-between visits - surveillance phone calls

Between the study visits, you will receive a phone call from the study doctor or the study coordinator to check how you are doing and see if you have any symptoms that might be a sign of relapse or infection. They will ask you a series of questions about your health and if you have any symptoms. If, after talking with you, they think that you might be relapsing or having an infection that should be treated, you will be asked to come to the clinic within the following week for a visit. **. If you do not have a standard of care visit scheduled during one of the 12 week visit windows, a visit will be done remotely by phone or video to collect information.**

For the WATCH group (those patients not receiving maintenance therapy) after randomization

You will have monthly clinic visits with a study doctor.

At every visit,

- you will have a physical exam
- we will take your vital signs (blood pressure, weight, temperature, respiration rate)
- you will give a urine sample
- you will have a blood draw done, for your care and sometimes for research (see the schedule of visits table for more info- each research blood draw is 24mls = a bit less than 2 tablespoons)
- if you are a woman who could become pregnant, we will do a urine pregnancy test
- the doctor will review your medications and how you feel
- every 4 months you will fill out a questionnaire about your quality of life

After Visit 5 (Week 16), the visits will decrease to every 6 weeks.

In-between visits - phone calls

Approximately two to three weeks after each study visit, you will receive a phone call from the study doctor or the study coordinator to check how you are doing. They will ask you a series of questions about your health and if you have any symptoms that might be a sign of relapse. If, after talking with you, they think that you might be relapsing, you will be asked to come to the clinic within the following week for a visit.

If you have a relapse when you are in the WATCH group, you will exit that surveillance group and be treated as needed by the doctor treating you for vasculitis. However, we would like to follow you and collect information and blood as scheduled during the rest of the study.

SCHEDULE OF VISITS for Maintenance Therapy group

	Physical exam	Review of your medications and how you feel	Quality of Life questionnaire	Blood draw for research	Urine pregnancy women only	Rituximab infusion *
Enrollment/ Screening visit	**X**	**X**	**X**	**X**	**X**	
Visit 1 Week 0	**X**	**X**	**X**	**X**	**X**	**X**
Visit 2 (8-12 weeks after V1)	**X**	**X**			**X**	
Visit 3 (8-12 weeks after V2)	**X**	**X**			**X**	
Visit 4 (8-12 weeks after V3)	**X**	**X**		**X[a]**	**X**	**X[a]**
Visit 5 (8-12 weeks after V4)	**X**	**X**			**X**	
Visit 6 (8-12 weeks after V5)	**X**	**X**	**X**		**X**	
Visit 7 (8-12 weeks after V6)	**X**	**X**		**X[a]**	**X**	**X[a]**
Visit 8 (8-12 weeks after V7)	**X**	**X**			**X**	
Visit 9 (8-12 weeks after V8)	**X**	**X**			**X**	
Visit 10 (8-12 weeks	**X**	**X**				

after V9 if months 24 not						
	Physical exam	**Review of your medications and how you feel**	**Quality of Life questionnaire**	**Blood draw for research**	**Urine pregnancy women only**	**Rituximab infusion ***
Visit 10 (8-12 weeks after V9 if months 24 not yet reached at V9)	**X**	**X**	**X**	**X[a]**	**X**	**X[a]**
Visit 11 (8-12 weeks after V10 if months 24 not yet reached at V10)	**X**	**X**			**X**	
Visit 12 (8-12 weeks after V11 if months 24 not yet reached at V11)	**X**	**X**			**X**	
Visit 13 (8-12 weeks after V12 if months 24 not yet reached at V11)	**X**	**X**		**X[a]**	**X**	**X[a]**

[a] Future rituximab infusion schedules will occur approximately every 6 months but timing will vary depending upon B cell levels and relapse symptoms. Blood draw for research will be done before the rituximab infusion

SCHEDULE OF VISITS for WATCH (No maintenance therapy group)

Phone calls will occur approximately 2 to 3 weeks after study visits.

	Physical exam	Review of your medications and how you feel	Quality of Life questionnaire	Blood draw for research	Urine pregnancy women only
Enrollment/ Screening visit	**X**	**X**	**X**	**X**	**X**
Visit 1 Week 0	**X**	**X**	**X**	**X**	**X**
Visit 2 Week 4	**X**	**X**			**X**
Visit 3 Week 8	**X**	**X**			**X**
Visit 4 Week 12	**X**	**X**		**X**	**X**
Visit 5 Week 16	**X**	**X**			**X**
Visit 6 Week 22	**X**	**X**	**X**	**X**	**X**
Visit 7 Week 28	**X**	**X**			**X**
Visit 8 Week 34	**X**	**X**		**X**	**X**
Visit 9 Week 40	**X**	**X**			**X**
Visit 10 Week 46	**X**	**X**	**X**	**X**	**X**
Visit 11 Week 52	**X**	**X**			**X**

	Physical exam	Review of your medications and how you feel	Quality of Life questionnaire	Blood draw for research	Urine pregnancy women only
Visit 12 Week 58	**X**	**X**		**X**	**X**
Visit 13 Week 64	**X**	**X**			**X**
Visit 14 Week 70	**X**	**X**	**X**	**X**	**X**
Visit 15 Week 76	**X**	**X**			**X**
Visit 16 Week 82	**X**	**X**		**X**	**X**
Visit 17 Week 88	**X**	**X**			**X**
Visit 18 Week 94	**X**	**X**	**X**	**X**	**X**
Visit 19 Week 100	**X**	**X**			**X**
Visit 20 Week 106	**X**	**X**	**X**	**X**	**X**

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

You might be treated with rituximab, azathioprine or mycophenolate mofetil.

Side Effects of Rituximab

Infusion Reactions

Rituximab can cause infusion reactions at the time of the treatment (1 in 5 patients are affected) and you may develop fever, chills and shivering. Other side effects uncommonly seen during the infusion are itching of the skin, sickness, tiredness, headache, breathing difficulties, sensation of the tongue or throat swelling, a runny nose, flushing, back pain and an irregular heart rate, although the nurses looking after you will be monitoring you closely. You will be given glucocorticoids and antihistamines through a vein prior to receiving the infusion, to minimize these side effects. Pre-existing conditions such as heart disease may be also be affected. The frequency of these reactions decreases during subsequent infusions. This drug rarely leads to a reduction in the level of healthy antibodies or white blood cells. Rituximab may rarely also cause abnormalities of your blood and affect liver function. In patients with autoimmune diseases, use of rituximab has been associated with two rare, but quite serious, skin reactions called toxic epidermal necrolysis and Stevens- Johnson syndrome. These skin reactions can be fatal. Some of the skin reactions occurred on the day of the infusion or within a few days of the infusion. However, in some cases, the event occurred weeks or months after infusion. You will be monitored for such reactions.

Other rare adverse effects which have been recorded after administration of rituximab include: rashes, difficulty sleeping, pain in muscles and joints, pain at the infusion site, anxiety, dizziness, tingling or numbness in hands or feet, sweating, abnormal taste, cough, reactivation of viral infection (for example, cold sores), heart problems.

Other Side Effects

Some patients developed new serious viral infections or had a worsening of chronic viral infections. Most, but not all, of these patients had cancer and they were on other anti-cancer treatments which made them more at risk. In some cases, these viral infections occurred over one year after rituximab treatment and resulted in death. A rare and severe viral infection called PML (progressive multifocal leukoencephalopathy), which can cause brain damage, such as memory loss, trouble thinking and blindness, is almost always fatal and has occurred in patients who received rituximab. The majority of these patients received rituximab in combination with chemotherapy (drugs that treat cancer) or as part of a bone marrow transplant. PML is currently believed to be very rare in vasculitis patients. Tell your doctor immediately if you, your family members or a health care provider notices if you are having any new or worsening medical problems, such as a new or sudden change in thinking, walking, strength, vision, or other problems that have lasted over several days. There are no known effective treatments for PML.

Your study doctor will discuss with you whether you are at high risk for exposure to Hepatitis B. One patient (of approximately 1000 rheumatoid arthritis patients treated with rituximab) developed a new infection with Hepatitis B virus and had symptoms of tiredness and yellow coloration of the skin. It is uncertain whether treatment with rituximab increased the risk for this infection. If you have Hepatitis B, you are not eligible for participation in this study.

Some patients with cancer who were treated with rituximab and chemotherapy had bowel problems including blockage and, in some cases, the bowel developed holes, which sometimes resulted in death.

Rituximab may lessen your body's ability to respond to live viral vaccinations (for example; measles, mumps or rubella). If you believe that it is necessary to have a non-live vaccination, you should have the vaccination 4 weeks before the first dose of study treatment.

Side Effects of Azathioprine

Azathioprine may cause nausea, diarrhea, vomiting, poor appetite, abdominal discomfort, headaches or liver upset. This drug can also cause rash, bone marrow suppression (and therefore increased risk of infection), or anemia (a low blood count). You should report any sore throat, abnormal bleeding or bruising to your study doctor. Azathioprine may also cause mouth ulcerations, and rarely gastrointestinal ulcerations, or sensitivity reactions such as fever, chills, muscle aches, and dizziness. It may also cause some hair loss.

You should wear sunscreen and avoid sunbathing, as there is an increased risk of skin cancer with this drug. Please avoid anyone with chicken pox or shingles while taking this drug.

Side Effects of Mycophenolate Mofetil

The most common side effects of mycophenolate mofetil are mild stomach upset (including diarrhea, nausea, vomiting, abdominal pain, constipation, loss of appetite and indigestion). This drug can also cause rash, bone marrow suppression (and therefore increased risk of infection), or anemia (a low blood count).

Risks Associated with Pregnancy

Because of the effects of these drugs there could be serious harm to unborn children or children who are breast-feeding. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a urine pregnancy test before entry into the study. You are asked to use a medically accepted method of birth control (such as implants, injectables, combined oral contraceptives, diaphragm, condom, spermicidal foam or the combination of any of the above) while you participate in the study. You should not become pregnant while you are taking these drugs. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist immediately.

Pregnancy tests will be done on all women who are able to get pregnant at the start of the study. This is part of the regular care for ANCA vasculitis, which means that you will have to pay for the pregnancy tests.

Risks of relapse

If we think that you are at risk for relapse, you will receive maintenance therapy. If we think you are in the “low-risk-of-relapse” group, you will be randomized to receive or not receive maintenance therapy. However, being in the “low-risk-of-relapse” group does not mean you will never have a relapse. It is possible that being placed into the group receiving no maintenance therapy will put you at risk for relapsing or for relapsing sooner than if you had received maintenance therapy. However, you will be monitored closely throughout the study period so that if you do have a relapse of disease, we will be able to treat it promptly.

Possible signs of relapse

Please call your study doctor or your treating doctor if you experience fever, severe joint pains, persistent nose bleeds, blood in the urine, coughing up blood or any other symptoms that you may find concerning.

Other Study Risks

Blood Draws and IV Therapy

The risks for blood drawing and insertion of an IV catheter are minimal and rare. They include:

• Minor discomfort, bleeding, and bruising at the site of the needle stick

• Feeling faint (like "passing out") during the blood draw or placing of the IV. If this occurs, the technician or nurse and other trained staff will be available to help you

• Infection, like redness, warmth, pain, swelling or foul-smelling discharge at the needle site

• Irritation or clotting of the vein (called superficial phlebitis) where the IV was can rarely occur with pain, redness, firmness at the needle site

• You may have some restriction of movement during the infusion time

Risks of Research Blood Samples

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick. However, usually, the research blood tubes will be taken at the same time as the other tubes, requiring no extra stick.

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

Live Virus Vaccinations

You should not receive ANY live virus vaccinations while in the study OR while receiving medications for maintaining suppression of your immune system. If for some reason you have received a live virus vaccine in the 4 weeks prior to, or after starting the study, administration of any maintenance immunosuppression medicines for your disease will be delayed by 4 weeks.

If you choose not to be in the study, what other treatment options do you have?

You do not have to be in this research study in order to receive treatment. Participants who receive treatment as part of the study will get the same treatment they would have if they were not part of the study. The only difference in being in the study is that we will use a new, unproven laboratory test to decide if you need maintenance therapy or not. Currently, there are no strict guidelines helping your kidney doctor to decide if you need maintenance therapy or not.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Will I receive any clinical results?

You will see all your lab results in your MyChart. The results from the CD5+ B cells tests are not validated yet and there will be a warning label about that in our MyChart when that result is provided.

Will you receive results from research involving your specimens?"

Tests may be done on these samples by study-approved researchers. You will not be informed of any of the results of the research testing.

The use of your samples may result in commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

How will information about you be protected?

Your personal information will be stored in a locked cabinet and in a secure password protected database.

You will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

We may use de-identified data and/or specimens from this study in future research without additional consent.

What is a Certificate of Confidentiality?
This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers may not disclose or use information, documents or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what study medications or tests you may be receiving as part of the study and know how to take care of you if you have other health problems or needs during the study. Additionally, the information may be shared with your medical insurance plan if the research services provided are billed to your insurance.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. The University of North Carolina at Chapel Hill has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. You do not give up any of your legal rights by signing this form.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

If you would like to withdraw from this study, you can contact the study staff listed on page 1. However, any samples or data that already have been placed in the research databases cannot be withdrawn.

Will you receive anything for being in this study?

You will be receiving parking coupons for each study visit.

Will it cost you anything to be in this study?

You will not have to pay to be in this study. You or your insurance company will be billed for the cost of all routine care provided during appointments when study visits are conducted. This means you and your insurance company will be billed for the visits, the lab tests, the treatment drug, the infusion costs, the pregnancy test (if applicable). You will not be billed for any additional research related tests.

When we take extra tubes of blood for research, you will not be billed for those tests.

If your study visit is conducted in the research unit, you will not be billed for an office visit.

If you receive a bill that you think is wrong, contact a researcher or study coordinator.

Who is sponsoring this study?

This research is funded by the National Institutes of Health (NIH). This means that the research team is being paid by the NIH for doing the study. The researchers do not, however, have a direct financial interest with the NIH or in the results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if you have questions about your rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

IRB Study # 18-2015

Title of Study: Tailoring Maintenance Therapy to CD5+ Regulatory B Cell Recovery in ANCA vasculitis

Principal Investigator: Vimal K. Derebail

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Participant Date Time

_____
Printed Name of Research Participant

_____ _____
Signature of Research Team Member Obtaining Consent Date Time

_____
Printed Name of Research Team Member Obtaining Consent

APPENDIX C: Script for patient scheduled monitoring calls

Days 15, 30, 45, etc.

"Hello,

This call is to check on how you are feeling and assess whether your vasculitis remains inactive

I will ask you a few questions about symptoms you may feel that could suggest the vasculitis is active or that you may have an infection. In answering, please think about the period of time since your last visit with Dr xxx. If you have any of these symptoms, please also tell me if this is new (in the last 2 weeks, or older) and how severe it is (mild, moderate or severe)"

1- Fever

2- Ear pain or change in hearing

3- Red or painful eyes

4- Bleeding from the nose, or sinus pain

5- Hoarseness, "air hunger", difficulty taking a deep breath

6- Cough or shortness of breath

   a. If cough, does anything come out? What color? Any blood in the sputum?

   b. If shortness of breath: is it with exertion (with walking, doing house chores or going up stairs for example), or even at rest? Is it worse at night? Do you feel that you get short of breath more easily than before?

7- Chest pain.

   a. How often, is it on exertion or even at rest? How long does it last? Does it change with position?

8- Any nausea or vomiting? How many times did you vomit? Was there any blood in it? When was the last time you vomited? Are you able to eat and keep your food down?

9- Any abdominal (belly) pain or diarrhea? Constipation?

   a. If diarrhea: are the stool soft, black and smelly? Is there any blood in the stool?

10- Any joint pain? Are the painful joints red, hot or swollen? How long do they last?

11- Any rash? If yes, where is it? Is it on both sides of the body or only one side?

   a. Is it painful?

   b. Any open sores

12- Any unusual headaches? Is it severe (cannot function)? Is it unusual for you?

13- Any new numbness, tingling or weakness in any limb (arms, legs, fingers, toes)?

14- Is there anything else you are concerned about that I did not ask you about?

If any of the above are answered positively:

“Have you called your doctor or the study doctor about this?”

- If yes: “what did the doctor tell you it was?
  - Did she/he prescribe any new medication? Any other change in medication?
  - Do you feel better since?”
- If no: I will relay this to the study doctor and he/she will get back with you and/or see you in clinic in the next 2-3 days.

If none of the questions are answered positively:

“I just want to remind you that your next appointment is on xxx at xxx time. Please remember to call us at (919) 4456-2630 to let us know if you are not feeling well between now and your next appointment. If it is after hours call the hospital operator and ask for the kidney doctor on call. Would you like me to remind you off the numbers to call?

If yes: study doctor # (919) 966-2561; Study coordinator: (919) 445-2730; hospital operator: (984) 974-4131

Thank you for your time.”

APPENDIX D: Case Report Forms

The following case report forms and logs will be used in this study:

1. Enrollment visit template CD5+
2. Enrollment Log CD5+
3. Phone call template CD5+
4. Randomization template CD5+
5. After randomization visit template CD5+
6. Concomitant Medications log CD5+
7. External reviewer relapse assessment template
8. Unexpected- Serious Adverse Event log CD5+
9. Delegation of responsibility log CD5+
10. Informed consent process documentation
11. Combined Damage Index CD5+
12. BVAS WG CD5+
13. Adverse Events Forms: AE and SAE