Synopsis

Title	Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis
Short Title	*Rituximab for ANCA-Associated Vasculitis*
Clinical Phase	II/III
IND Sponsor	DAIT, NIAID
Study Conduct	ITN
Protocol Chairs	Ulrich Specks, MD John H. Stone, MD
Accrual Objective	200 participants
Accrual Period	30 months
Study Duration	The common closing date will be 18 months after the last participant is enrolled in the trial.
Study Design	This is a randomized, multicenter, double-masked, placebo-controlled trial in participants with severe ANCA-associated vasculitis (AAV). Two hundred participants will be randomized in a 1:1 ratio to the experimental arm or the control arm of the trial.
Primary Study Objective	To determine the efficacy of rituximab (375 mg/m^2, four weekly infusions) and glucocorticoids in the induction of complete remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 off glucocorticoid therapy.
Primary Endpoint	The percentage of participants who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper at 6 months after randomization.
Secondary Objectives	1. To compare the safety profile of rituximab with that of conventional therapy. 2. To assess the superiority of rituximab as compared to conventional therapy. 3. To determine the duration of complete remission induced by four infusions of rituximab (375 mg/m2). 4. To determine if participants with severe AAV who are treated with rituximab can achieve clinical tolerance as defined in section 9.
Secondary Endpoints	1. The adverse event rate, expressed as adverse events per participant-year during the 6, 12, and 18 months after randomization for the following adverse events combined: • Death (all causes) • Grade 2 or higher leukopenia or thrombocytopenia • Grade 3 or higher infections

- Hemorrhagic cystitis (grade 2 or lower needs confirmation by cystoscopy)
- Malignancy
- Venous thromboembolic event (deep venous thrombosis or pulmonary embolism).
- Hospitalization resulting either from the disease or from a complication due to study treatment.
- Infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions (including cytokine-release allergic reaction).
- Cerebrovascular accident (CVA).

2. The two-sided 95% CI of the percentage of participants who have a BVAS/WG of 0 and have successfully completed the glucocorticoid taper by 6 months after randomization and two-sided 95% CI of the difference between the two arms.
3. The duration of complete remission, the time to limited and/or severe flare after complete remission (see section 3.7 for the definitions of limited and severe flare) in the two treatment groups.
4. The percentage of participants who meet the criteria for clinical tolerance, as defined in section 1.6.4, at 12 and 18 months after randomization and at the common closing date.

Tertiary Objectives

1. To determine the percentage of participants in complete remission at 12 and 18 months after randomization.
2. To assess other measures of efficacy and safety of rituximab in participants with severe AAV.
3. To determine the effect of rituximab on markers of inflammation and specific immune parameters through a series of detailed mechanistic studies (section 9).

Tertiary Endpoints

1. The percentage of participants in complete remission at 12 and 18 months after randomization.
2. The cumulative BVAS/WG AUC during the 6, 12, and 18 months after randomization.
3. The percentage of participants who achieve and maintain partial remission (defined as having a BVAS/WG of 1 or 2) at months 6, 12, and 18.
4. The percentage of participants who achieve a BVAS of 0 on prednisone <10 mg/day at 6, 12, and 18 months after randomization.
5. The percentage of participants who achieve complete remission after blinded crossover.
6. The cumulative steroid dose between groups for participants at 6, 12, and 18 months.

7. The number of severe flares in participants at 6, 12, and 18 months.
8. The number of limited flares in participants at 6, 12, and 18 months.
9. The percentage of participants who withdraw from the study or treatment because of drug intolerance (e.g., emesis, infusion reactions).
10. Laboratory markers of inflammation (ESR and CRP).

Inclusion Criteria

Potential participants must meet all of the following criteria to be eligible for enrollment in the study:

1. Age: They must be 15 years of age or older.
2. Weight: They must weigh at least 40 kg.
3. Diagnosis type: They must be diagnosed with WG or MPA according to the definitions of the Chapel Hill Consensus Conference (Appendix 7). The maximum number of participants with MPA diagnosis shall not exceed 50% of all participants.
4. Screening diagnosis: They must be newly diagnosed patients, or they must have a disease flare that fulfills inclusion criteria 5, 6, and 7.
5. Disease activity: They must have active disease with a BVAS/WG ≥ 3 that would normally require treatment with CYC.
6. Disease severity: They must have severe disease, i.e., one or more of the major BVAS/WG items listed in Table 2, or disease severe enough to require treatment with CYC.
7. ANCA status: They must be positive for either PR3-ANCA or MPO-ANCA at the screening
8. Contraception contract: They must be willing to practice medically acceptable contraception (e.g., combination barrier method and spermicide, hormonal therapy) until one full menstrual cycle (women) or 3 months (men) have passed after the discontinuation of AZA/AZA placebo and at least 1 year after the first rituximab/rituximab placebo infusion.
9. Pregnancy reporting contract: They must be willing to report pregnancies (females and male's partners) that occur at any time during the trial and up to 1 year after completion of study therapy.
10. Breastfeeding contract: If female, they must be willing to refrain from breastfeeding throughout the trial.
11. Compliance contract: They must be willing to comply with study procedures, including completion of all baseline assessments and mechanistic studies within 14 days of starting intravenous steroids for a disease flare, with the assistance of a caregiver if necessary.
12. Competence: They must be willing and able to provide informed consent.

Exclusion Criteria

Patients who meet any of these criteria will not be enrolled in this study:

1. Diagnosis: They are diagnosed with Churg Strauss syndrome as defined by the Chapel Hill Consensus Conference (Appendix 7).
2. Disease severity:
    a. Limited disease: They have limited disease that would not normally be treated with CYC.
    b. Severe disease: They require mechanical ventilation because of alveolar hemorrhage.
3. Co-morbidities:
    a. Allergies: They have a history of severe allergic reactions to human or chimeric monoclonal antibodies or murine protein.
    b. Infection (systemic): They have an active systemic infection.
    c. Infection (deep space): They have, or have been diagnosed as having, a deep-space infection, such as osteomyelitis, septic arthritis, or pneumonia complicated by empyema or lung abscesses, within 6 months of randomization.
    d. Infection (blood borne): They have active hepatitis B or active hepatitis C or a documented history of HIV, hepatitis B, or hepatitis C.
    e. Liver disease: They have acute or chronic liver disease that is deemed sufficiently severe to impair their ability to participate in the trial.
    f. Renal disease: They have a history of documented anti-GBM disease.
    g. Malignancy: Active or history of malignancy in the last 5 years. Individuals with squamous cell or basal cell skin carcinomas and individuals with cervical carcinoma in situ may be enrolled if they have received curative surgical treatment.
    h. Uncontrolled disease: They show evidence of other uncontrolled disease, including drug and alcohol abuse, that could interfere with participation in the trial according to the protocol.
4. Diagnostics:
    a. WBCs: They have a white blood cell count that is less than 4,000/mm^3.
    b. Platelets: They have a platelet count that is less than 120,000/mm^3.
    c. Liver function tests: They have an ALT or AST level

greater than 2.5 times the upper limit of normal that cannot be attributed to underlying AAV disease.

d. Creatinine: They have a serum creatinine level greater than 4.0 mg/dL that is attributed to renal failure from a current flare. Individuals with stable renal failure from the previous episode of active disease may be included in the study if the flare involves other organ systems.

e. Human antichimeric antibodies: They have had any history of HACA formation.

f. Pregnancy test: positive

5. Treatments

a. CYC (adverse effects): They are intolerant to CYC—i.e., they have previously suffered the adverse effects of conventional therapy that preclude CYC use. These effects may include CYC-induced hemorrhagic cystitis, bone marrow hypoplasia, or malignancy.

b. CYC (recent use): They have used CYC, oral or IV, within the past 4 months unless they started oral CYC not more than 1 week prior to enrollment (see section 5.6.2).

c. Monoclonal antibodies: They have had any previous treatment with rituximab or Campath-1H.

d. Prohibited medications: They have used any of the prohibited medication listed in section 5.6.2.

e. Plasma exchange: They have been treated with plasma exchange within the 3 months preceding the screening visit.

f. Vaccines: They have had a live vaccine fewer than 4 weeks before randomization.

Summary of Study Procedures

Screening: procedures to establish inclusion/exclusion criteria.

Baseline: procedures to establish baseline values for efficacy outcome (BVAS/WG) and other outcomes of interest: immediately after randomization but before receiving any treatment.

Remission induction phase: from the first administration of study treatment through month 6. BVAS/WG scores, use of prednisone, and the occurrence of selected adverse events obtained during this period will be analyzed for the primary and secondary analyses. Participants may be crossed over to the other treatment arm should they be considered treatment failures (see section 3.8.1.1).

Remission maintenance phase: beginning after month 6 through the common closing date (18 months after enrollment of the last participant). Efficacy and safety outcomes obtained during this period will be analyzed for secondary endpoints including induction of tolerance. Participants who experience severe flares during this period

will be treated with open label rituximab (see section 3.8.1.2). After month 18, the investigator may treat participant based on best medical judgment.

Treatment Description

Glucocorticoids. Glucocorticoids will be given to both treatment arms. Participants will receive a 1-day course of intravenous glucocorticoids, followed by oral prednisone; the IV glucocorticoids may be repeated up to a maximum of 3 days at the discretion of the investigator. The prednisone will be tapered so that by month 6 all participants in clinical remission will be off glucocorticoids. The guidelines for intravenous glucocorticoid therapy and the prednisone tapering are provided in section 5.3.1.

Remission induction phase (baseline i.e. date of randomization through months 3 to 6): The experimental arm will receive intravenous infusions of rituximab (375 mg/m2/week times 4) and daily CYC placebo plus oral prednisone. The control arm will receive CYC (2 mg/kg, with doses modified for renal dysfunction) and four weekly infusions of rituximab placebo plus oral prednisone.

Remission maintenance phase (months 3 to 6 through month 18): The experimental arm will switch from daily CYC placebo to AZA placebo. The control arm will switch from daily CYC to AZA (2 mg/kg/day). After completion of the month 18 visit, treatment will be according to best medical judgment.

Statistical Consideration and Sample Size

Sample size assumptions: A 70% complete remission rate in the control group and the experimental group at 6 months after randomization; a noninferiority limit of 20% on the difference in the complete remission percentage between the experimental arm and the control arm; a one-sided 0.025 level test; a 10% dropout rate. These assumptions require 100 participants in each arm to have 83% power to conclude noninferiority.

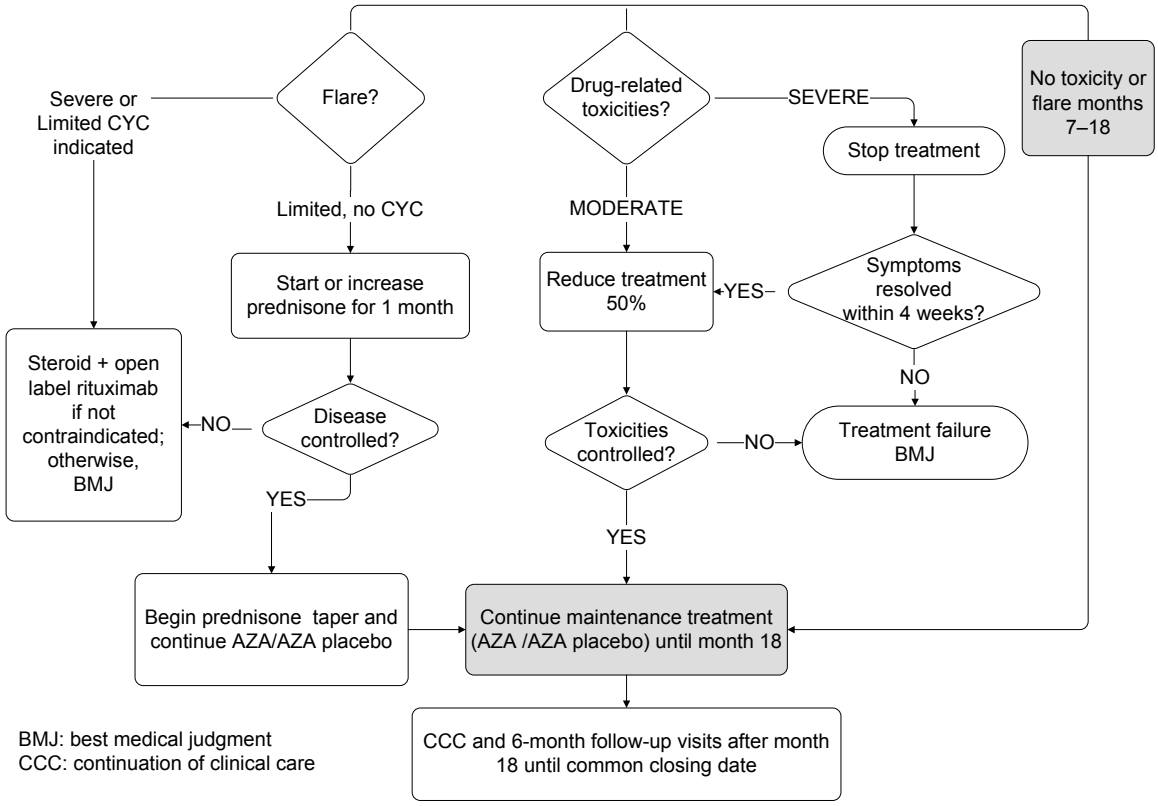
Primary efficacy analysis: The difference in the percentage of participants who attain complete remission in the experimental group versus the percentage of participants who attain complete remission in the control group, which will be obtained using a t-distribution multiplier with a one-sided 97.5% confidence interval. The lower bound of this confidence interval around the difference in proportions will be used to assess noninferiority and superiority. If the lower bound is below −20%, noninferiority will be rejected. If the lower bound is above −20%, noninferiority will be concluded. If the point estimate for the complete remission rate in the experimental arm is lower than that of the control arm, the point estimate for the control arm complete remission rate must be at least 40% in order to meet the claim of noninferiority for rituximab. If the lower bound of the difference is above zero, superiority will be concluded on the condition that the lower bound of the two-sided 95% confidence interval of the complete remission rate at 6 months in the experimental arm is greater than or equal to 50%.

Safety analysis: The rate of the selected adverse events (see secondary endpoints above). A Poisson regression model will be used to compare

the difference of the above adverse events between the two treatment groups.

Other analyses: Kaplan-Meier and Cox proportional hazards model will be used to evaluate differences in the time-to-event endpoints between the two groups. Linear regression models will be used to evaluate changes in continuous outcomes. Repeated measure analyses will be used to account for the within-person correlation.

Months 7–18 AZA/AZA placebo



BMJ: best medical judgment
CCC: continuation of clinical care