WGET Protocol (Version 3.0)

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WGET Protocol (Version 3.0)

Distribution history

Version 1.0 (22 December 1999): distributed to protocol committee, NIAMS, FDA, Immunex Corporation

Version 1.1 (07 February 2000): distributed to Research Group, NIAMS, FDA, DSMB, Immunex Corporation

Version 2.0 (26 April 2001): distributed to Research Group, NIAMS, FDA, DSMB, Immunex Corporation

Version 3.0 (13 February 2002): distributed to Research Group, NIAMS, FDA, DSMB, Immunex Corporation
§2.2 The number of centers participating in this trial is decreased from 9 to 8. We anticipate that this decision will have minimum impact upon patient recruitment in this trial; the decrease in centers changes rate of enrollment required of each clinic from a rate of 8 patients/year to a rate of 9 patients/year.

§3.1 There are several amendments to the inclusion criteria:

- A new inclusion criterion relates to the use of birth control is added: “Willingness of men or women of childbearing potential to practice an adequate method of birth control while on the experimental treatment and for 3 months after the experimental treatment is stopped”. The adequate and inadequate birth control methods are detailed in the consent form. In the Manual of Operations, we will include instructions for the clinic coordinators to follow up with patients during the 3 month period after the experimental treatment is stopped, to encourage compliance with this criterion.

- A new inclusion criterion relates to breast-feeding is added: “Willingness to refrain from breast-feeding while on the experimental treatment and for 3 months after the experimental treatment is stopped”. Whenever appropriate, the clinic coordinator will follow up with patients during the 3 month post-trial period, to ensure compliance with this criterion.

- Alcohol use during the trial is now mentioned in the inclusion criteria rather than in the exclusion criteria. The previous exclusion criterion regarding alcohol reads: “Alcohol use in excess of 2 ounces of 100 proof liquor or 1 beer (or the equivalent) per week. All alcohol use will be discouraged during this trial”. The new inclusion criterion reads: “Willingness to limit alcohol consumption to one alcoholic drink per week while taking MTX. All alcohol use will be discouraged during this trial”.

§3.2 There are several amendments to the exclusion criteria:

- A previous exclusion criterion: “Treatment of any WG therapy for more than 28 days prior to randomization” is deleted.

- We have broadened the language with regard to liver dysfunction as an exclusion criterion. The former exclusion criterion reads: “Known acute or chronic liver disease. We will test patients with elevated transaminases for
viral hepatitis prior to trial entry. Those with positive tests for hepatitis B and/or C antigens will be excluded”. The revised criterion reads “Acute or chronic liver disease that is deemed sufficiently severe to impair the patient’s ability to participate in the trial.”

- We have broadened the exclusion criterion with regard to previously diagnosed malignancies and is now read: “Current evidence of malignancy, or history of a malignancy diagnosed within last 5 years. Patients with squamous or basal cell carcinomas of the skin and patients with cervical carcinoma in situ may be enrolled if they have received curative surgical treatment.” The time limit indicated in the previous version of the protocol was 6 months, rather than 5 years. The latter time limit is consistent with the policies followed in other trials of etanercept.

- A new exclusion criterion is added: “Previous therapy with specific therapies directed against tumor necrosis factor, e.g., etanercept or infliximab.”

§4.1 We have included methods to guard against unmasking in this trial. These include: (1) the clinic coordinator, rather than the study physician, is to administer the first dose of experimental treatment, (2) patients will be instructed to discuss any difficulties with the injections or injection site reactions with the clinic coordinator or study nurse. Patients will be instructed not to discuss these issues with the study physician, and (3) at followup visits, injection sites and other randomly chosen sites will be covered with gauze in order to prevent the physicians from becoming aware of injection site reactions.

§4.1.1 The revised protocol states that the experimental medication may be administered “…by the patients themselves or by a designated caregiver (e.g., a spouse)” (Wording in italics is new).

§4.1.1 We have provided more specific guidelines regarding the suspension of experimental treatment in the event of suspected or culture-proven infections: “Suspected or culture-proven bacterial, protozoal, or fungal infections, or in the event of viral infections deemed serious by the study physician (e.g., influenza, cytomegalovirus). In the event of such occurrences, the length of the experimental treatment cessation shall be at the discretion of the study physician.”

§4.1.3.2 We have deleted the stop criterion that required patients to be withdrawn from the experimental treatment if they were required to suspend use of the experimental treatment for more than 28 days. The Stop Criterion has been amended to indicate that cessation of the experimental treatment will occur in the event of a second (rather than a third) severe disease flare.
§4.1.4 We have included a new section specifying our policy for unmasking treatment assignments. This section reads: “Treatment assignments will be masked to all clinical personnel and patients during the trial. All patients will be informed of their treatment assignments at the followup visit that corresponds to the common study closeout. If the experimental treatment is terminated before the common study closeout, treatment assignments will not be unmasked. In the event that there is a need to unmask a treatment assignment during the trial, the study physician will contact the WGET Chairman, Dr. John Stone, to discuss the need for unmasking.”

§5 Concomitant medications:

- The dose of trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis carinii* pneumonia has been corrected. In the revised protocol, all patients will receive prophylaxis with single-strength trimethoprim/sulfamethoxazole tablets daily.
- The Vitamin D dose has been corrected to 400 IU per day (rather than 500 IU).

§7.7 The Vasculitis Damage Index has been added as an outcome measure, and will be assessed at baseline and every 6 months.

§7.8 Patient Global Assessment of WG activity has been added as an outcome measure, and will be completed at every study visit

Consent Form changes:

- Procedures (paragraph 2): We have provided more details about the use of blood samples saved in the course of this trial. Because some of the ancillary studies performed in concert with this trial may involve tests to determine genetic susceptibility to Wegener’s granulomatosis, to good or bad outcomes, and to responsiveness to therapy, and other questions related to the disease under study, we have specified that blood samples may be used for these purposes. We emphasize, however, that the blood samples will be used only to investigate questions related to Wegener’s granulomatosis. Furthermore, the blood samples sent to the central repository will be labeled only with study codes, and not patient identifiers. The language of this new part of the Consent Form reads as follows: “The blood and urine tests will be repeated at regular intervals throughout the study. Some of the blood tests (drawn at intervals not shorter than 6 weeks) and urine tests will be used for studies related to the cause, prognosis, and disease mechanisms of WG. These studies may involve the testing for the presence of genes (DNA) and investigations of blood factors (e.g., antibodies or novel inflammatory proteins) that may influence the risk of getting WG, the risk of having a severe form of the disease, and the chance of responding to treatment.”
Risks/Discomforts (paragraph 3): We have updated to language on alcohol use in the trial to reflect the revised language of the protocol. We have replaced the sentence reading “You should not drink more than 2 ounces of 100 proof liquor or 1 beer or its equivalent per week” with the statement: “In order to participate in this trial, you must be willing to limit your intake of alcohol to 1 alcoholic drink or less per week”.

Risks associated with the use of Enbrel (paragraph 6): we have included specific language regarding “adequate” and “inadequate” methods of birth control: “All men and all women of childbearing potential must practice an adequate method of birth control while participating in this trial and for 3 months after stopping the experimental treatment. Adequate methods of birth control include: sexual abstinence (not having sex), oral contraceptives (“birth control pills”) or other hormone-based method, the combined use of condom and diaphragm, the combined use of diaphragm and spermicide, tubal ligation, and vasectomy. Inadequate methods include: the rhythm method, withdrawal, condoms (alone), diaphragm (alone), and an intra-uterine device (IUD).”

Version 2.0 (26 April 2001): Protocol revised and distributed to Research Group, NIAMS, FDA, DSMB, and Immunex Corporation

§3.2 The following Exclusion criterion was added: “History of multiple sclerosis or other neurological symptoms suggesting a demyelinating syndrome.”

§4.1.3.1 The following criterion was added to the list of reasons for temporary withholding of the experimental treatment: “Moderate or severe bone marrow suppression (i.e., cytopenia) that does not respond within 14 days to adjustment of conventional immunosuppressive therapies.” Experimental treatment should be withheld if patients develop cytopenia that does not improve within 14 days of adjusting the dose of the standard treatments.

§4.1.3.2 The following criterion was added to the list of reasons for termination of the experimental treatment: “Development of neurological symptoms that (following appropriate evaluation) are diagnostic or suggestive of demyelinating syndrome.” Patients who during the trial develop any neurological symptoms suggesting a demyelinating syndrome should discontinue experimental treatment immediately.

§7.7 Birmingham Vasculitis Damage Index the last sentence has been changed and it reads now: “VDI will be assessed at baseline and at all followup visits.”

§7.10 Adverse events - the following clarifications were added: All events that result in or prolong an existing hospitalization should be reported regardless of presumed association to WG or experimental treatment. All such events should be reported as Safety Reports (not just on AE log).
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§9.3 Adverse events - a phrase “regardless of presumed association to experimental treatment was deleted.

§11 Sample size calculations and data analysis sections were revised; selection of adjustment covariates for the evaluation of treatment effect was explained (based on the method by Canner). Reference #9 - (Canner PL) was added.

Appendices D, E, F, H, and I - were updated.

Consent Form changes:

- **Section PROCEDURES**
  - Paragraph 1 - (page 2) two bullets were added “A medical history and physical examination” and “You will fill out a questionnaire about the impact of your disease on your quality of life (this will take approximately 10 minutes)”
  - Paragraph 2 - The word future was inserted into the following sentence: “Some of your blood will be stored for purposes of future research studies specifically related to WG”
  - Paragraph 3 - The sub-heading “Treatment Assignment was added. Also, the phrase “visit your doctors” was replaced with the phrase “have a study visit”; and a sentence was added: “Each appointment will take approximately 1-2 hours of time”.
  - Paragraph 4 - lines 2-3, the phrase “will be kept by a group of doctors whose job it is to monitor the safety of the study’ was replaced with the phrase “will be kept by the study coordinating center”.

- **Section RISK/DISCOMFORTS**
  - Page 3, paragraph 1, under the sub-heading Risks Associated With Standard Medicines Used To Treat WG or death” was added.
  - Page 4, paragraph 2, last sentence. The phrase “you will be withdrawn from the study” was replaced with “you will discontinue the experimental medication, but will continue to be followed as a patient in the trial”.

- **Section BENEFITS**
  - Paragraph 1, page 5, the length of time the study treatment will be provided was clarified: The last sentence now reads: “There is no guarantee that the study medication will be provided beyond the 12 to 42 month study period”. The sentence in the previous version indicated that the study period was only 12 months.

- **Section Reasons For Withdrawal From The Study Without Your Consent**
  - Page 5, (f) was to read “The study is canceled by the National Institutes of Health or the Food and Drug Administration...”. Previously, the sentence read “The study is
canceled by the Food and Drug Administration or the company (Immunex Corporation) supplying the drugs”. Under our amended contract with Immunex, the company cannot cancel the trial.

- **Section Costs or Payment to You**
  - Page 6, the sentence “You will receive no payment for being in this study” was replaced with “You will be reimbursed $25.00 for each regularly-scheduled trial visit for costs incurred in participating in this study”
  - Page 6 two paragraphs with new language related to confidentiality were added. The new paragraph reads: “We are collecting data for the purpose of this study. We will keep the data at your clinic and at the study coordinating center in Baltimore, Maryland. Your research records will be kept confidential to the extent permitted by the law. You will be identified by a study number and personal information from your records will not be released without your written permission. Unless required by law, only the team of investigators involved in this study, the Institutional Review Boards of universities participating in the study, the National Institutes of Health or its representatives, the Data and Safety Monitoring Board, the United States Food and Drug Administration, and the pharmaceutical company providing the medication will have access to your study records and associated medical records. Medical information from the study will be made available to your physician unless you specify otherwise. If a health condition is detected during the study, you will be told about it and the information will be given to your doctor or clinic. A Safety Officer has been named to monitor the safety of this clinical trial. He will review data routinely to assess safety concerns. Your records from this study will be retained for seven years. Your identity will not be revealed in any publication or release of results. This study is authorized by Privacy Act 42 United States Code 241.

  “If you have any questions about any part of the study or your rights as a volunteer, a WGET staff person will be on hand to answer them before you sign this consent form. If you have any questions at any time you may call Dr. Stone at 410-614-4905, or any of the staff persons listed at the beginning of this document. Before you sign this form, please ask any questions on any part of this study that is unclear to you.”

- **Section: IF YOU ARE HURT BY BEING IN THE STUDY**
  - Page 7, the language of the original Consent Form was supplemented. The full section now reads: “If you think you have been hurt by being in the study, or not treated fairly, you should call the Joint Committee on Clinical Investigation at (410) 955-3008 to
receive help or advice, including help finding medical care if needed. The Johns Hopkins University, (CCC University or University of XXX), and the Federal government do not have any program to pay you if you are hurt or have other bad effects which are not the fault of the study doctors. If you are injured as a result of being in this study, medical treatment will be available. For further information about this, you may call the office of the Joint Committee on Clinical investigation.”

The revisions to the WGET Consent form are summarized below; additions are indicated in bold, and deletions are indicated with strikethroughs:

- section PROCEDURES, page 2, paragraph 2 – the word “specifically” has been deleted from the following sentence: “Some of your blood will be stored for purposes of future research studies specifically related to WG.” The NIH/NIAMS sponsors suggested that the word “specifically” technically limited ancillary studies using these samples to only studies of WG. In the future, the samples may also be used for studies of other forms of vasculitis or other vascular diseases.

- section RISK / DISCOMFORTS, Risk associated with the use of Enbrel™

Several modifications were made to this section:

- page 3, paragraph 2 – the following statement was added: “To date, the incidence of cancer in patients receiving etanercept has been found to be the same as that of untreated people. Results of clinical trials do not show that Enbrel™causes cancer or autoimmune diseases or that it increases infections.”

- page 3, paragraph 3 – the phrase “such as diabetes” has been deleted. The WGET DSMB suggested that since WGET does not exclude diabetic patients, the phrase “such as diabetes” is unnecessary. Additionally, the following information (in bold) has been added:

> “It is still possible that Enbrel™ may make infections worse and could result in life-threatening complications. The infections may occur in any body system. Serious infections, including deaths from infection, have been reported with the use of etanercept. Many of these infections occurred in patients with diseases that tend to weaken the body’s ability to fight infection, such as diabetes. In some patients, very low blood cell counts have been reported. If you develop signs and symptoms of a significant infection or persistent fever, bruising, bleeding, or very pale skin, you should contact your physician immediately. to determine whether you should interrupt drug dosing.”
“Rare neurologic events, including multiple sclerosis, have been reported. If you are found to have multiple sclerosis, or develop weakness or visual disturbances, notify your physician.”

“Other serious conditions that have been reported in patients receiving Enbrel™ include: heart problems, such as heart failure and heart arrest; high and low blood pressure; circulation, bleeding and clotting problems; delayed healing; stroke; shortness of breath; digestive system disorders (including intestinal perforation); kidney problems; back or joint pain; diabetes; weakness; and rash. These serious conditions were rare and it is unclear whether or not etanercept was the cause.”

• section ALTERNATIVES TO PARTICIPATION IN THIS STUDY, Confidentiality page 6, paragraph 1. The following changes were made (in the middle of the paragraph):

“Unless required by law, only the team of investigators involved in this study, the Institutional Review Boards of universities participating in the study, the National Institutes of Health or its representatives, the Data and Safety Monitoring Board, and the United States Food and Drug Administration will have access to your study and associated medical records. The pharmaceutical company providing the medication will have access to your study data sets that do not include personal identifiers.”

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§4.2.3 A new section was added regarding azathioprine: “After a minimum of 3 months of CYC therapy, patients with severe disease may be treated according to the protocol for limited WG if their disease control is sufficient. Such patients with a serum creatinine of greater than 2.0 mg/dL are not eligible to receive MTX therapy. In such cases, patients will be treated with azathioprine (AZA) and will remain on the trial protocol. Patients who experience serious intolerable side-effects of MTX such as pneumonitis or persistently elevated hepatic transaminases are also eligible to receive AZA. At the time of evaluation for trial entry, patients with limited WG and a serum creatinine of greater than 2.0 mg/dL (e.g., secondary to non-WG causes) are not eligible for enrollment.”

“The AZA treatment should be initiated at a starting dose of 50 mg daily. At the physician’s discretion, the dose may be increased over 4-6 weeks to a maximum of 2.5mg/kg/day. Doses will be rounded up to the nearest 25 mg interval.” Changes to AZA treatment are described in 4.2.3.2.
§5 Concomitant medications: The guidelines for administration of trimethoprim/sulfamethoxazole (T/S) as prophylaxis against Pneumocystis carinii pneumonia have been revised. Patients may either receive single-strength T/S tablets daily OR double-strength T/S three times a week. 

Also, guidance for treatment with folinic acid was added. Patients who experience cytopenias, oral ulcers, or other complications presumed secondary to MTX may be treated with either 2 mg of folic acid daily, OR up to 5 mg/week of folinic acid (administered the day after MTX).

§6 Management of disease flares: The following clarification was added: “After the occurrence of two limited flares or after the occurrence of 1 severe and 1 limited flare, a patient may be maintained on a dose of prednisone not to exceed 10 mg/day (dose chosen at the discretion of the study physician) designed to maintain control of disease and minimize corticosteroid side-effects.”

§7.5 A section on screening for latent tuberculosis infection was added: “All WGET patients should undergo a purified protein derivative (PPD) skin test for latent tuberculosis infection. Patients who have previously received the Bacille Calmette-Guérin (BCG) vaccination should still be tested with a PPD test, unless the BCG was administered within the past 3 years. Patients who have undergone PPD testing within 6 months are exempt. If patients do not wish to be screened for LTBI, they may refuse PPD testing following a discussion with the study physician.

Patients enrolled prior to the implementation of protocol version 3.0 should be screened with a PPD test at the next scheduled followup visit. All future patients who plan to enroll in WGET after the implementation of protocol version 3.0 should undergo PPD testing at the baseline visit. Guidelines for the screening of patients, the interpretation of PPD skin tests, and the management of patients following testing are provided in the WGET Manual of Operations.”

§7.10 Adverse events – the following clarification was added: “An adverse event is any untoward medical occurrence in a patient ever administered the experimental treatment (etanercept or placebo) that does not necessarily have a causal relationship with treatment” (change underlined).

Appendix B Added azathioprine therapy to standard treatment algorithm for patients with severe WG.

Appendix C Added azathioprine therapy to standard treatment algorithm for patients with limited WG.
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Appendix D  Updated required schedule for Vasculitis Damage Index completion.  Added PPD screening as a required procedure.

Appendix E  Updated required schedule for Vasculitis Damage Index completion.

Appendix G  Added list of resource centers.

Appendix I  Updated the prototype consent form to include language on tuberculin skin testing for LTBI and options for banking blood samples for future research studies related to WG.

Appendix J  Included a prototype WGET Assent form for Minors.

Appendix K  Updated the glossary to include AZA (azathioprine), LTBI (latent tuberculosis infection), PPD (purified protein derivative) and T/S (trimethoprim-sulfamethoxazole).

Consent form changes:

Section PROCEDURES

- Paragraph 1 - one bullet was added - “A skin test for tuberculosis”
- Paragraph 2 - a new paragraph was added - “Because patients treated for WG have suppressed immune systems, an infection called tuberculosis (TB) is a concern. This is why we would like to perform a skin test for TB. If the test is positive, further tests such as a chest x-ray may be required. If TB is confirmed, your/your child’s doctor will prescribe medications. You/your child may still participate in this trial if you/your child refuse(s) to have the skin test for TB.”
- Paragraph 4 - a new paragraph was added - “You may still participate in this trial without having extra blood drawn and stored for research purposes. Please read the following statements, and mark and initial the box of your choice:
  ________ (subject initials) “I permit my blood samples to be collected, stored, and used in future research studies related to WG”.
  ________ (subject initials) “I do not permit my blood samples to be collected, stored, and used in future research studies related to WG”.


Abstract

The Wegener’s Granulomatosis Etanercept Trial (WGET) is a phase II/III, randomized, double-masked, placebo-controlled clinical trial. The primary objective of the trial is to evaluate the efficacy and safety of etanercept (Enbrel™; Immunex Corporation, Seattle, WA) in the induction and maintenance of disease remissions for patients with Wegener’s Granulomatosis (WG), when used in conjunction with standard treatment. A secondary objective is to develop a specimen bank of blood samples that may be used to address basic questions regarding the etiology, pathophysiology, and monitoring of WG.

The sample size is 180 patients, to be recruited from 8 clinical centers in the United States over a 30-month period. Patients are assigned randomly to receive either etanercept or placebo in an allocation ratio of 1:1. Randomization is stratified by clinic and disease severity (limited versus severe). Every patient enrolled will have a Birmingham Vasculitis Activity Score (BVAS) of at least 3, ensuring unequivocally active disease.

In addition to either etanercept or placebo, all patients receive standard treatment for WG depending on severity of the disease. Those with limited WG receive methotrexate and corticosteroids, and those with severe WG receive cyclophosphamide and corticosteroids. After the patients’ disease is controlled with therapy (i.e., the standard treatment plus either etanercept or placebo), the standard medications are tapered according to regimens designed to ensure patient safety, diminish morbidity associated with the standard medications, and test the efficacy of etanercept in sustaining disease remissions.

Followup evaluations will be conducted at 6 weeks and 3 months after randomization, and every 3 months thereafter. All randomized patients, regardless of whether or not they remain on their assigned treatments, will be followed until the common closing date of the trial, defined as 12 months after enrollment of the last patient.

The primary outcome measure for this trial is the remission achieved and maintained (sustained remission) in the two treatment groups. A sustained remission is defined as a minimum of 6 months of BVAS of 0 (i.e., 3 consecutive visits excluding the F01 visit). The primary analyses will be performed on an intention-to-treat basis.
1. Wegener’s Granulomatosis

Wegener’s Granulomatosis (WG) is characterized by inflammation, granuloma formation, geographic tissue necrosis, and vasculitis of multiple organ systems. The disease is the prototype of disorders associated with anti-neutrophil cytoplasmic antibodies (ANCA), and is among the most common forms of systemic necrotizing vasculitis. In the absence of treatment, the 6-month mortality rate of this disease is 50%. Although WG has a predilection for involving the upper respiratory tract, lungs, and kidneys, it may strike virtually any organ.

For the purpose of this trial, WG has been sub-divided into 2 categories of disease severity: limited and severe. Limited WG is defined as that occurring in a patient who meets the modified American College of Rheumatology (ACR) criteria for diagnosis of WG (see Section 3.1, Inclusion criteria, below) but who does not have disease that poses an immediate threat to either a critical individual organ or to the patient’s life. Severe WG is defined as that which is not classifiable as limited disease. Detailed definitions of limited and severe disease are found in Appendix I.

1.1. Current approach to treatment

The initial treatment of WG generally consists of a “cytotoxic” agent (e.g., cyclophosphamide or methotrexate) and high-dose corticosteroids. Corticosteroids alone, even in high doses, usually fail to control WG. Although a study from the pre-chemotherapy era showed that corticosteroids prolonged the median survival from 5 months to 12.5 months, more recent data from the National Institutes of Health (NIH) indicated that corticosteroids alone controlled the disease in only 2 of 58 patients. When used in combination with a cytotoxic agent, corticosteroids may often be tapered off approximately 6 months after the start of treatment. Some centers have used alternate day steroid doses after several months of daily administration.

Treatment regimens using either cyclophosphamide (CYC) or methotrexate (MTX) are associated with high risks of disease relapse following the achievement of remission. In a longitudinal case series of CYC-treated patients from the NIH, only 37.5% achieved stable, disease-free remissions with their initial treatment. Half of the patients who did achieve remissions later suffered flares of their disease, some while still on therapy, others during tapering of therapy. In the experience with WG at Johns Hopkins University, 0 of 19 patients treated with MTX and prednisone maintained durable remissions after tapering off medications. The requirement for retreating patients experiencing disease flares with CYC, MTX, and corticosteroids results in considerable cumulative morbidity from therapy.

Overall, current therapy for WG is poorly tolerated, with high incidences of opportunistic infections, bone marrow suppression, malignancies, and other morbidity. Furthermore, even among patients who achieve remissions initially, subsequent flares are common. The most important
problem confronting WG patients today is the absence of a well-tolerated, effective therapy for the maintenance of remission.

1.1.1. Cyclophosphamide

Cyclophosphamide (CYC) is used for patients with severe WG, as defined in this protocol. Most centers in the US use daily oral CYC, but intermittent (monthly) intravenous CYC is preferred at some centers.51 The proper duration of treatment with CYC remains poorly defined. CYC has substantial short-term and long-term toxicity.

For patients receiving CYC as therapy for WG, short-term side effects pose daunting problems. In a recent French trial comparing oral and intravenous administrations of CYC, 54% of the patients developed opportunistic infections.25 During the trial, 18% of the patients died from side effects of therapy. Overall, 38% of the patients enrolled in the trial died (during a 2.5-year period). Numerous other studies in WG have confirmed the hazards of using CYC to induce remission in this disease.

The long-term side effects of CYC treatment regimens are also substantial. In a series of 158 patients with WG treated at the NIH,26 42% treated with daily oral CYC suffered permanent morbidity related to treatment. There was an 11-fold increased risk of lymphoma or leukemia, and a 33-fold increase in the likelihood of bladder cancer. Among patients treated with daily oral CYC and followed for up to 15 years, the overall incidence of bladder cancer was 16%.68 Forty-three percent of the patients developed hemorrhagic cystitis, and 57% of the women of childbearing potential became infertile as the result of treatment. Cyclophosphamide (CYC) is used for patients with severe WG, as defined in this protocol. Most centers in the US use daily oral CYC, but intermittent (monthly) intravenous CYC is preferred at some centers.51 The proper duration of treatment with CYC remains poorly defined. CYC has substantial short-term and long-term toxicity.

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1.1. Current approach to treatment

1.1.1. Cyclophosphamide

the patients developed hemorrhagic cystitis, and 57% of the women of childbearing potential became infertile as the result of treatment.26

1.1.2. Methotrexate

Methotrexate (MTX) is less effective than CYC and is also associated with significant toxicity. Nevertheless, because of the morbidities associated with CYC use, the combination of MTX and prednisone is now the standard of care for patients with limited WG, as defined in this protocol.13,27,65,67 Despite its usefulness in limited disease, however, MTX has not been evaluated thoroughly in cases of severe WG. Progression of the disease to severe glomerulonephritis during treatment with MTX has been described in up to 29% of MTX-treated patients, although low doses of corticosteroids were used in that study.13 MTX is also contraindicated in patients with significant renal insufficiency (serum creatinine > 2.0 mg/dL).27 Finally, treatment protocols using MTX rather than CYC also are associated with significant morbidity. In an NIH study, for example, 10% of the patients developed *Pneumocystis carinii* pneumonia while using MTX.65

1.2. Experimental treatment

1.2.1. Etanercept

Etanercept (Enbrel™; Immunex Corporation; Seattle, WA) is a fusion protein consisting of two recombinant p75 tumor necrosis factor (TNF) receptors linked to the Fc portion of human IgG1.48 The medication is a powerful antagonist of TNF, binding to and inactivating this cytokine. TNF plays a critical role in WG as well as in some other chronic inflammatory conditions.3,4,5,7,64 For the past 5 years, etanercept has been tested extensively in human trials, including clinical trials in rheumatoid arthritis (RA), juvenile RA, geriatric (age > 65) patients with RA, Crohn’s disease, human immunodeficiency virus (HIV) infection, congestive heart failure, allograft rejection, sepsis syndrome, and healthy human subjects.35 There exist substantial data about the safety of etanercept in humans, as well as its optimal dosing from phase I, II, and III trials. Etanercept has been approved by the Food and Drug Administration (FDA) for the treatment of RA and juvenile RA.

1.2.2. Etanercept’s mode of TNF inhibition

TNF is a critical mediator of local inflammation.1 The release of TNF leads to activation of vascular endothelium, including adhesion molecule expression and upregulation of class II major histocompatibility molecules. These events orchestrate the recruitment of inflammatory cells, immunoglobulins, and complement. In addition, TNF stimulates the release of other pro-
1.2. Experimental treatment

1.2.2. Etanercept’s modes of TNF inhibition

Inflammatory cytokines, including interleukin (IL)-1, IL-6, and IL-8. Because of its dimeric receptor configuration, etanercept has substantially higher affinity for TNF than the naturally-occurring monomeric soluble receptor. The immunoglobulin-like Fc structure of etanercept also prolongs the half-life of the molecule \textit{in vivo}. Etanercept interrupts the TNF-associated inflammatory cascade, by several mechanisms:

- Competitive inhibition of binding by TNF to its native TNF receptors which reside on the surfaces of inflammatory cells
- Acting as a cytokine “carrier” for TNF, rendering it biologically unavailable even though it prolongs the molecule’s serum half-life
- Modulation of biological events mediated by “downstream” molecules, whose functions are regulated by TNF. For example, in RA, etanercept decreases the levels of IL-1, IL-6, E-selectin and intercellular adhesion molecule-1 (ICAM-1)\textsuperscript{35}
- In addition to binding TNF, etanercept binds and disrupts the function of lymphotoxin-\(\alpha\) (LT-\(\alpha\)), another important inflammatory cytokine in the TNF family\textsuperscript{5}

1.2.3. Rationale for anti-TNF treatment in WG

The following evidence suggest that TNF plays a major role in WG:

- Granuloma formation, the pathologic hallmark of the disease, is inhibited completely by the absence of TNF\textsuperscript{38}
- Active WG is associated with a dramatically upregulated Th1 cytokine pathway, a pathway in which the role of TNF is pivotal\textsuperscript{43}
- Transcription of the TNF gene is enhanced in peripheral blood mononuclear cells from patients with WG\textsuperscript{14}. CD4\textsuperscript{+} T cells from patients with WG produce elevated levels of TNF\textsuperscript{43}
- Serum levels of both TNF and its soluble receptors, p55TNFR and p75TNFR, are elevated in patients with active WG\textsuperscript{37,52}. Levels of the p55TNFR, an excellent surrogate for TNF levels, correlate with WG activity as measured by the Birmingham Vasculitis Activity Score\textsuperscript{52}. With the induction of remission, levels of these molecules normalize
- Immunohistochemistry, polymerase chain reaction, and \textit{in situ} hybridization studies of renal biopsies from patients with WG confirm that TNF-positive cells infiltrate histologically active renal lesions. Such cells are also present within the walls of arteries and arterioles in acute vasculitic lesions\textsuperscript{53}
- Neutrophils are important in the pathophysiology of WG. \textit{In vitro} priming of activated neutrophils with TNF markedly enhances the ability of ANCA to stimulate neutrophil degranulation, fueling the leukocytoclastic vasculitis associated with this disorder\textsuperscript{19,61}
1.2. Experimental treatment

1.2.3. Rational of anti-TNF treatment in WG

In most studies, a distinctive feature of WG is its strong association with the ANCA response to proteinase 3 (PR3), a constituent of neutrophil granules. TNF synergistically induces PR3 expression on both neutrophils and possibly endothelial cells. TNF also facilitates the presentation of PR3 by macrophages. These actions increase the accessibility of PR3 for binding with ANCA, and may therefore contribute directly to the pathophysiology of WG in most patients.

TNF inhibition has been remarkably successful in treating even refractory forms of similar conditions associated with chronic inflammation, including Crohn’s disease and RA.

1.2.4. Etanercept in pre-clinical models

Etanercept has undergone extensive testing in a variety of animal models of disease, including collagen-induced arthritis in mice; antigen-induced arthritis in rats, cachexia in TNF transgenic mice, murine models of hypersensitivity pneumonitis and allergic asthma; and respiratory distress syndrome. Although no entirely appropriate animal model of WG exists, other pre-clinical models that are particularly pertinent to the use of etanercept in WG (by virtue of the disease’s characteristic granulomatous pathology) include:

- Inhibition of inflammatory granuloma formation in the lungs of mice following the intraperitoneal administration of Schistosoma mansoni eggs. The mechanism of this inhibition is interference with TNF-inducible ICAM-1 expression.
- Reduction of hepatic granuloma formation in a murine model of schistosomiasis.

1.2.5. Effectiveness of anti-TNF modalities in human immune-mediated disease

Two methods of inhibiting TNF have been tested thoroughly in human diseases. As of December 1999, two drugs (each representing one of these approaches) have been approved by the FDA for use in chronic inflammatory diseases: infliximab (in Crohn’s disease and RA), and etanercept (in RA and juvenile RA).

1.2.5.1. Crohn’s disease

Crohn’s disease, a granulomatous disorder with many pathological similarities to WG, is a chronic inflammatory disorder of the gastrointestinal tract. Two monoclonal antibodies to TNF have demonstrated the effectiveness of neutralizing TNF in the management of Crohn’s disease, even in patients with treatment-resistant disease (a genetically-engineered human antibody - CDP571,
1.2. Experimental treatment

1.2.5. Effectiveness of anti-TNF modalities in human immune-mediated disease

1.2.5.1. Crohn’s disease

Celltech Therapeutics, Ltd., UK; and a chimeric antibody-infliximab, Remicade™, cA2; Centocor; Malvern, PA). In a randomized, double-masked, placebo-controlled trial of CDP571 in patients with Crohn’s disease, the median disease activity score declined by nearly 50% within 2 weeks of a single intravenous infusion (P = 0.0003).66 No significant change in disease activity occurred in the placebo group.

In a similar trial of infliximab in Crohn’s disease, patients with treatment-resistant disease, 65% responded within one month to single intravenous doses of infliximab, compared with only 17% patients in the placebo group (P = 0.001).69 One-third of the patients randomized to infliximab achieved remissions after only one dose.

1.2.5.2. Rheumatoid arthritis

Both of these monoclonal antibodies to TNF also demonstrate striking effectiveness in patients with severe RA, a disorder sometimes complicated by rheumatoid vasculitis.17,57 In trials of anti-TNF therapy in RA, the American College of Rheumatology definition of a 20% response was the principal outcome measure.21

In a randomized, double-masked comparison of high-dose infliximab to placebo, 19 of 24 patients in the infliximab group responded to treatment with a single infusion, compared with 2 of 24 patients in the placebo group (P < 0.0001).17 The maximum mean improvements in the number of tender or swollen joints was greater than 60% for patients who received one dose of infliximab. In another trial, the combination of infliximab and MTX was synergistic.45 Patients treated with infliximab and MTX maintained 70-90% reductions in swollen joint counts, tender joint counts, and C-reactive protein levels throughout the 26-week course.

In Phase II and III trials of etanercept, the drug was safe, well-tolerated, and associated with remarkable improvement in joint inflammation.49,50,73 In a Phase II trial of 180 patients, 75% of the group who received 25 mg etanercept injections twice a week (b.i.w.) responded by 3 months, compared with 14% in the placebo group (P < 0.001).49 A dose-response curve was evident as etanercept doses increased from 0.25 mg/m² b.i.w. to 2 mg/m² b.i.w. to 16 mg/m² b.i.w. (the last dose is equivalent to 25 mg, the b.i.w. dose used in this trial). The mean percent reduction in the number of tender or swollen joints was 61% in the 25 mg etanercept group, compared with 25% in the placebo group (p = 0.001). The time to response among patients treated with etanercept was swift: generally 4 weeks in the 25 mg group.

These findings were extended in a Phase III trial involving 234 RA patients who had failed a series of disease-modifying agents.50 In that trial, the patients were randomized to receive placebo or etanercept (either 10 mg or 25 mg b.i.w.). Ninety percent of the patients enrolled had failed MTX...
1.2. Experimental treatment

1.2.5. Effectiveness of anti-TNF modalities in human immune-mediated disease

1.2.5.2. Rheumatoid arthritis

treatment for their RA before entering the trial, illustrating their disease’s severity. Nevertheless, at 6 months, 59% of the patients in the 25 mg etanercept group and 51% in the 10 mg etanercept group had responded, contrasted with only 11% of the patients in the placebo group (P < 0.001). In the 25 mg etanercept group, the mean percent reduction in the number of tender or swollen joints at 6 months was 56% and 47%, respectively, compared with 6% and –7% in the placebo group (P < 0.05). In open-label extension trials, durable responses to etanercept have been shown for up to 2 years.

Responses to etanercept were not confined to clinical measures of arthritis severity. Rather, patients also reported dramatic improvements in quality of life, as measured by the Health Assessment Questionnaire (HAQ). All administered subdomains of the HAQ improved among etanercept-treated patients compared to controls, including Disability, Vitality, Mental Health, and General Health Status. In a Phase III trial, the perception of General Health Status among etanercept-treated patients (either 10 or 25 mg b.i.w.) improved by 50% over 12 months. In comparison, over the same time period, the General Health Status perception of placebo-treated patients declined by 2%.

1.2.6. Etanercept in combination with MTX

In a Phase III trial investigating patients with refractory RA, etanercept was proven to be safe when used in conjunction with MTX. In the trial, adverse events among patients treated with etanercept and MTX included only minor injection site reactions and upper respiratory symptoms. In addition to the safety of this drug combination, 71% of the patients treated with etanercept/MTX responded to therapy (compared with 27% in the placebo/MTX group, P < 0.001). Using a more rigorous standard of 50% improvement, the response rates were 39% in the etanercept group and 3% in the placebo group (P < 0.001).

1.2.7. Dose selection

The dose of etanercept chosen for this trial (25 mg b.i.w.) is identical to that used in Phase II and III trials in RA. Dose escalation studies in RA, Crohn’s disease, sepsis, HIV, and CHF have demonstrated the safety of this dose in humans, as well as its efficacy in the inhibition of TNF. In a phase I trial of etanercept in Crohn’s disease, dose-limiting headaches were reported with 50 mg loading doses. The dose of 25 mg b.i.w. was well-tolerated in WG patients enrolled in an open-label trial, conducted to confirm the safety of this drug in WG prior to initiating this randomized trial.
WGET Protocol (Version 3.0)

1. Wegener’s Granulomatosis

1.2. Experimental treatment
1.2.7. Dose selection

The expense of etanercept ($12,000/year) demands a rigorous assessment of its efficacy in the treatment of WG. The safety of the agent has been established by extensive experience with the use of etanercept in humans. The drug has been tested in clinical trials in over 1,000 patients with RA, and more than 50,000 patients have received the drug following approval of the drug by the FDA for RA treatment.
2. Objectives and design

2.1. Objectives

The primary objective of the Wegener’s Granulomatosis Etanercept Trial (WGET) is to evaluate the efficacy and safety of etanercept in the induction and maintenance of disease remissions for patients with WG, when used in conjunction with standard treatment.

A secondary objective of the trial is to develop a specimen bank of blood samples that may be used to address basic questions regarding the etiology, pathophysiology, and monitoring of WG.

2.2. Design

The trial is a Phase II/III, randomized, double-masked, placebo-controlled clinical trial. It is a multicentered trial with a parallel treatment design. Patients are assigned randomly to receive either etanercept or placebo in an allocation ratio of 1:1. Randomization is stratified by clinic and disease severity (limited versus severe). Both patients and clinic personnel are masked to treatment assignment. The sample size is 180 patients, to be recruited at 8 clinical centers (Appendix ?) in the United States over a 30-month period. The primary measure of efficacy is the rate of achieved and maintained remissions, as measured by the Birmingham Vasculitis Activity Score (BVAS) for WG. Every patient enrolled must have a minimum BVAS of 3, ensuring unequivocally active disease.

In addition to either etanercept or placebo, all patients receive standard treatment regimens for WG. Those with limited WG receive MTX and corticosteroids, and those with severe WG receive CYC and corticosteroids. After the patients’ disease is controlled with therapy (i.e., the standard treatment regimen plus either etanercept or placebo), the standard treatment will be tapered according to regimens designed to ensure patient safety, diminish morbidity associated with the standard treatment, and test the efficacy of etanercept in maintaining disease remissions.

Followup evaluations will be conducted at 6 weeks and 3 months after randomization, and then every 3 months thereafter. All randomized patients, regardless of whether or not they remain on their assigned treatments, will be followed until the common closing date of the trial, defined as 12 months after enrollment of the last patient. The primary analyses will be performed on an intention-to-treat basis.
WGET Protocol (Version 3.0)

3. Enrollment and randomization

Recruitment, assessment of eligibility, and enrollment are to be performed at clinics certified to participate in the trial. Once it has been determined that a patient is eligible for the trial, the specific details of the trial should be discussed and explained to the patient. Patients considering enrollment in the trial will be given the consent form and other information, and permitted time (preferably overnight) to decide whether to enroll in the trial. It is important to give patients adequate time to consider the decision, in order to ensure informed consent. The consent statement should be signed before eligibility or baseline data are collected. All baseline evaluations are to be conducted within 7 days prior to randomization. Patients unable to complete the baseline evaluations will be ineligible to enroll.

3.1. Inclusion criteria

- Minimum weight of 40 kg
- Diagnosis of WG, with the exclusion of infections, malignancies, systemic autoimmune disorders, and other forms of vasculitis that may mimic WG
- Presence of at least 2 of the 5 modified American College of Rheumatology (ACR) criteria for a diagnosis of WG. The modified ACR criteria are:26,34,43,43,44
  - Nasal or oral inflammation, defined as the development of painful or painless oral ulcers, or purulent or bloody nasal discharge
  - Abnormal chest radiograph, defined as the presence of nodules, fixed infiltrates, or cavities
  - Active urinary sediment, defined as microscopic hematuria (> 5 red blood cells per high power field) or red blood cell casts
  - Granulomatous inflammation (in the extravascular or perivascular area) and/or necrotizing vasculitis (with or without granulomatous features)
  - Positive serum ELISA for ANCA directed at serine proteinase 3 (PR-3)
- BVAS of 3 or greater within 28 days of baseline evaluation. This may include either the presence of one or more major items (3 points each) or the presence of three or more minor items (1 point each)
- Willingness and ability to comply with treatment and followup procedures, with the assistance of a caregiver if necessary
- Willingness of men or women of childbearing potential to practice an adequate method of birth control (e.g., abstinence, combination barrier method and spermicide, hormonal therapy) while on the experimental treatment and for 3 months after the experimental treatment is stopped
- Willingness to refrain from breast-feeding while on the experimental treatment and for 3 months after the experimental treatment is stopped
3.1. Inclusion criteria

- Willingness to limit alcohol consumption to one alcoholic drink per week while taking MTX. All alcohol use will be discouraged during this trial
- Complete all baseline procedures within 14 days prior to randomization
- Signed and dated consent form

3.2. Exclusion criteria

- Presence of an active systemic infection
- White blood cell count less than 4,000/mm3
- Platelet count less than 120,000/mm3
- Creatinine greater than 2.0 mg/dL secondary to non-WG causes (e.g., hypertensive nephropathy) for a patient with limited disease (Note that patients with severe WG and a creatinine > 2.0 mg/dL are eligible for enrollment)
- Acute or chronic liver disease that is deemed sufficiently severe to impair the patient's ability to participate in the trial
- Current evidence of malignancy, or history of a malignancy diagnosed within last 5 years. Patients with squamous or basal cell carcinomas of the skin and patients with cervical carcinoma in situ may be enrolled if they have received curative surgical treatment
- Positive serum pregnancy test for women of childbearing potential
- Previous therapy with specific therapies directed against tumor necrosis factor, e.g., etanercept or infliximab
- History of multiple sclerosis or other neurological symptoms suggesting a demyelinating syndrome

3.3. Randomization

Randomization is stratified by clinic and disease severity (limited or severe WG). **Limited WG** is defined as that occurring in a patient who meets the modified American College of Rheumatology (ACR) criteria for the diagnosis of WG (see complete definition in Appendix H), but who does not have disease that poses an immediate threat to either a critical individual organ or to the patient’s life. **Severe WG** is defined as that which is not classifiable as limited disease. Treatment assignments are generated in permuted blocks of varying lengths. The randomization schedule is generated, written, and controlled by the Coordinating Center (CC), and is designed to yield an expected assignment ratio of 1:1 between the 2 treatment groups, etanercept, and placebo. The assignment schedule is provided to Almedica, which will label and package etanercept and matching placebo. Treatment assignments will be masked to both patients and clinic personnel.

Clinic personnel will obtain treatment assignments from the CC as each new patient is enrolled. Treatment assignment is communicated by facsimile transmission (fax). Before a treatment assignment is released, all baseline procedures must be completed, eligibility must be reviewed by the...
3.3. Randomization

CC, and the consent form must be signed and dated. Once an assignment has been released to the clinic, the patient is counted in the assigned treatment group for the primary analysis, regardless of subsequent treatment or adherence to study protocol. Knowledge of the treatment assignment is restricted to designated CC personnel.
4. Study treatment plan

Throughout this protocol the term “experimental treatment” refers to either etanercept or placebo. “Standard treatment” refers to cyclophosphamide (CYC), methotrexate (MTX) and corticosteroids. “Study treatment” refers to the combination of experimental treatment and standard treatment. Patients receive the experimental treatment in conjunction with the standard treatment.

4.1. Experimental treatment

Experimental treatment will be provided by Immunex Corporation. The two experimental treatment groups are:

- Etanercept
- Placebo

Patients will begin their assigned experimental treatment as soon as possible after randomization. The first dose should be administered at the clinic with the help of clinic personnel, usually the clinic coordinator. The study physician does not administer the medication, in order to avoid the possibility of unmasking. Patients will be instructed to discuss any difficulties with the injections or injection site reactions with the clinic coordinator or study nurse. Patients will be instructed not to discuss these issues with the study physician. At followup visits, injection sites and other randomly chosen sites will be covered with gauze in order to prevent the physicians from becoming aware of injection site reactions. Procedures for covering sites are described in the WGET Manual of Operations.

Barring the occurrence of a stop criterion (Section 4.1.3.2), patients will continue to receive their assigned experimental treatment for the duration of the trial. Treatment will be administered as described below.

4.1.1. Etanercept

Etanercept is to be taken at a dose of 25 mg, subcutaneously twice a week. It is reconstituted with 1 mL bacteriostatic water before use. It is to be administered in the form of injection by the patients themselves or by a designated caregiver (e.g., a spouse).
4.1. Experimental treatment

4.1.2. Placebo

The placebo consists of a lyophilized powder containing 40 mg of mannitol, 10 mg of sucrose, and 1.2 mg of TRIS. The injection volume of the placebo is standardized by dilution with bacteriostatic water (1 mL per dose), and is equal to that of etanercept dose (25 mg). The placebo injection is to be administered by the patients themselves or by a designated caregiver (e.g., a spouse), according to the same schedule as patients assigned to etanercept, twice a week.

4.1.3. Changes in experimental treatment

If an injection site reaction occurs, the site of injection should be changed. If the injection site reactions are so severe or persistent as to be intolerable to the patient, the experimental treatment should be terminated.

Patients are to remain on their assigned experimental treatment in the event of severe flare or the occurrence of certain drug toxicities. However, the occurrence of some events will require temporary discontinuation or termination of the experimental treatment. These events are described in the following sections.

4.1.3.1. Temporary discontinuation of treatment

At the discretion of the study physician, the experimental treatment should be withheld if any of the events listed below occurs. Reasons for temporary withholding of the experimental treatment include:

- Suspected or culture-proven bacterial, protozoal, or fungal infections, or viral infections (e.g., influenza, cytomegalovirus) deemed serious by the study physician. In the event of such occurrences, the length of the experimental treatment cessation shall be at the discretion of the study physician.
- Moderate or severe bone marrow suppression (i.e., cytopenia) that does not respond within 14 days to adjustment of conventional immunosuppressive therapies.
- Other events that (in the opinion of the study physician) are serious and cannot be ascribed to WG or to concomitant medications. Such events may lead to permanent discontinuation (termination) of the experimental treatment upon review by the DSMB.
4.1.3.2. Termination of treatment

The following are the criteria for termination of the experimental treatment:

- Injection site reactions so severe or persistent as to be intolerable to the patient
- Occurrence of 2 severe disease flares. Severe flares are defined as the new occurrence of one or more major BVAS items. Major items have a * on the BVAS scoring sheet
- Severe cytopenia (WBC count < 3,000/mm³ or a platelet count < 80,000/mm³) that does not recover after withholding either MTX or CYC for up to 28 days
- Development of neurological symptoms (following appropriate evaluation) that are diagnostic or suggestive of demyelinating syndrome
- Aplastic anemia
- Newly recognized malignancy (with the exception of basal and squamous cell malignancies of the skin, or cervical carcinoma in situ that can be excised and cured surgically)
- Pregnancy
- Patient’s request
- Study physician believes that withdrawal is in the patient’s best interests
- Noncompliance, as judged by the study physician

Patients whose experimental treatment is terminated will continue to be followed according to the data collection schedule until the common closing date of the trial.

4.1.3.3. Events that do not require termination of treatment

The following events will not require temporary withholding or termination of the experimental treatment:

- Hypertension
- Congestive heart failure
- Diabetes mellitus
- Insufficiency fracture of bone
- Avascular necrosis
- Corticosteroid-induced myopathy
- Corticosteroid-induced cataracts
- Corticosteroid-induced glaucoma
- Psychosis or profound mood alteration induced by corticosteroids
- Alopecia
- Nausea
- Hemorrhagic cystitis
4.1. Experimental treatment

4.1.3. Changes in experimental treatment

4.1.3.3. Events that do not require termination of treatment

- Pneumonitis associated with one of the standard medications
- Oral ulcers/dermatitis
- Allergic reaction to trimethoprim/sulfamethoxazole (T/S) (in the event of an allergy to T/S, dapsone 100 mg p.o. q day may be substituted)

4.1.4. Unmasking treatment assignments

Treatment assignments will be masked to all clinical personnel and patients during the trial. All patients will be informed of their treatment assignments at the followup visit that corresponds to the common study closeout. If the experimental treatment is terminated before the common study closeout, treatment assignments will not be unmasked. In the event that there is a need to unmask a treatment assignment during the trial, the study physician will contact the WGET Chairman, Dr. John Stone, to discuss the need for unmasking. Data regarding the date and reason for unmasking will be collected. Followup will continue for the patients whose treatment has been unmasked.

4.2. Standard treatments

All patients receive standard treatment for WG depending on disease severity (limited or severe WG). Those with limited WG receive MTX and corticosteroids. Those with severe WG receive CYC and corticosteroids. After the patients’ disease is controlled with therapy (i.e., the standard treatment plus either etanercept or placebo), the standard medications are tapered according to regimens designed to ensure patient safety, diminish morbidity associated with the standard medications, and test the efficacy of etanercept in sustaining disease remissions.

4.2.1. Methotrexate

4.2.1.1. Administration

Patients with limited WG (or with severe disease who switched from CYC to MTX) initially receive methotrexate (MTX) and corticosteroids, in addition to either etanercept or placebo. The MTX treatment should be initiated at a starting dose of 0.25 mg/kg/week given orally (e.g., 15 mg/week for a 60-kg individual). The initial dose will not exceed 20 mg/week for any patient. Doses will be rounded up to the nearest 2.5 mg interval. If the treatment is well tolerated after one week, the MTX dose will be increased by 2.5 mg a week up to a dose of 0.35 mg/kg/week, not to exceed a weekly dosage of 25 mg for any patient. In the event of nausea induced by oral MTX, the
4.2. Standard treatments

4.2.1. Methotrexate

4.2.1.1. Administration

Drug may be administered either in divided p.o. doses (q 12 hours) or subcutaneously. Patients on MTX will also receive folic acid, 1 mg p.o. q day. A flowsheet for the treatment of patients with limited disease is displayed in Appendix C.

### 4.2.1.2. Changes in treatment

Patients will be treated with MTX until they have been in remission for 12 months. Remission is defined as a BVAS of 0. At that time, a MTX taper will begin, with a reduction in the MTX by 2.5 mg/month.

The MTX treatment regimen will be modified, interrupted, or terminated if any of the following events occurs:

- Moderate or severe bone marrow suppression (WBC less than 4,000/mm³, hematocrit less than 28%, or platelet count less than 120,000/mm³)
- Moderate or severe liver function test abnormalities (AST or ALT greater than 2 times the upper limit of normal)
- Serum creatinine greater than 2 mg/dL
- Pneumonitis that cannot be attributed to causes other than the MTX
- Infections
- Nausea and/or vomiting
- Malignancy
- Other intolerable side effects

Complete guidelines for the modification, interruption, termination, and restarting of MTX treatment are provided in the WGET Manual of Operations.

### 4.2.2. Cyclophosphamide

#### 4.2.2.1. Administration

Patients with severe WG initially receive CYC and corticosteroids, in addition to either etanercept or placebo. The CYC treatment should be initiated at a dose of 2 mg/kg, p.o. q day. A lower dose of CYC may be used if renal insufficiency is present (see algorithm in Section 4.2.1.2). The investigator treating the patient has the option of administering up to 4 mg/kg of CYC for the first 3 days of treatment.
4.2. Standard treatments

4.2.2. Cyclophosphamide

4.2.2.1. Administration

In the event that a patient is unable to take CYC orally (e.g., an intubated patient), the medication may be administered intravenously on the same daily schedule and dosing regimen. Patients on CYC will be instructed to drink eight 8-ounce glasses of fluid per day. A flowsheet for the treatment of patients with severe disease is displayed in Appendix B.

4.2.2.2. Changes in treatment

All patients with severe disease should receive at least 3 months of treatment with CYC. Patients whose disease severity is reclassified as limited (see Appendix H) or in remission (defined as a BVAS of 0) after a minimum of 3 months of treatment will discontinue CYC and begin MTX. Reclassified patients with a serum creatinine greater than 2.0 mg/dL (which precludes treatment with MTX) will be treated with azathioprine (2 mg/kg/day) and will remain on the trial protocol.

If a patient classified as having severe disease at entry has not been reclassified as having limited disease or has not achieved a remission after 6 months of CYC therapy, the patient will remain on CYC and be treated according to best medical judgement. In the absence of contraindications, the patient will continue CYC as well as the assigned experimental treatment. The patient also will continue followup according to the data collection schedule, with additional visits as necessary for optimal care.

CYC doses will be adjusted according to the level of renal function, estimated by calculating the creatinine clearance ($\text{CL}_{\text{cr}}$) ($\text{CL}_{\text{cr}} = (120 – \text{patient’s age})/\text{serum Cr (mg/dL)}$ for men; $\times 0.8$ for women). Guidelines for CYC dose adjustment for renal function are as follows:

<table>
<thead>
<tr>
<th>$\text{CL}_{\text{cr}}$ (mL/minute)</th>
<th>Daily CYC Dose (mg/kg/day)</th>
</tr>
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<tr>
<td>$\geq 100$</td>
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<td>50-99</td>
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<tr>
<td>25-49</td>
<td>1.2</td>
</tr>
<tr>
<td>15-24</td>
<td>1.0</td>
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<tr>
<td>$&lt; 15$ or dialysis</td>
<td>0.8</td>
</tr>
</tbody>
</table>
4.2. Standard treatments
4.2.2. Cyclophosphamide
4.2.2.2. Changes in treatment

Treatment with CYC should be modified, interrupted, or terminated if any of the following events occur:

- Moderate or severe bone marrow suppression (WBC less than 4,000/mm³, hematocrit less than 28% because of marrow suppression, or platelet count less than 120,000/mm³)
- Moderate or severe liver function test abnormalities (AST or ALT greater than 2 times the upper limit of normal)
- Hemorrhagic cystitis, defined as gross or microscopic hematuria plus cytoscopy showing bleeding, atrophy, pallor, telangiectasia, or contracture of the bladder mucosa
- Pneumonitis that cannot be attributed to causes other than CYC
- Infections requiring hospitalization
- Nausea and/or vomiting
- Malignancy
- Other intolerable side effects

Complete guidelines for the modification, interruption, termination, and re-starting of CYC treatment in the event of side effects (e.g., cytopenia or infection) are provided in the WGET Manual of Operations.

4.2.3. Azathioprine

4.2.3.1. Administration

After a minimum of 3 months of CYC therapy, patients with severe disease may be treated according to the protocol for limited WG if their disease control is sufficient. Such patients with a serum creatinine of greater than 2.0 mg/dL are not eligible to receive MTX therapy. In these cases, patients will be treated with azathioprine (AZA) and will remain on the trial protocol. Patients who experience serious intolerable side-effects of MTX such as pneumonitis or persistently elevated hepatic transaminases are also eligible to receive AZA. At the time of evaluation for trial entry, patients with limited WG and a serum creatinine of greater than 2.0 mg/dL (e.g., secondary to non-WG causes) are not eligible for enrollment.

The AZA treatment should be initiated at a starting dose of 50 mg daily. At the physician’s discretion, the dose may be increased over 4-6 weeks to a maximum of 2.5 mg/kg/day. Doses will be rounded up to the nearest 25 mg interval.
4.2.3.2. Changes in Treatment

Following the start of AZA, patients will be treated with AZA until they have been in remission for 12 months. Remission is defined as a BVAS of 0. At that time, an AZA taper will begin, with a reduction in the AZA dose by 25 mg/month.

The AZA treatment regimen will be modified, interrupted, or terminated if any of the following events occurs:

- Moderate or severe bone marrow suppression (WBC less than 4,000/mm³, hematocrit less than 28%, or platelet count less than 120,000/mm³)
- Moderate or severe liver function test abnormalities (AST or ALT greater than 2 times the upper limit of normal)
- Pancreatitis that cannot be attributed to any cause other than AZA
- Infections
- Nausea and/or vomiting
- Malignancy
- Other intolerable side effects

Complete guidelines for the modification, interruption, termination, and restarting of AZA treatment are provided in the WGET Manual of Operations.

4.2.4. Corticosteroids

4.2.4.1. Administration

All patients enrolled in the trial receive corticosteroids. At the discretion of the study physician, a patient with severe disease may be treated initially with 1 gram of methylprednisolone i.v. q day for 3 days. Following this, the patients will be converted to daily oral prednisone at doses ranging from 0.5 mg/kg to 1 mg/kg (not to exceed 80 mg/day), or the intravenous equivalent for patient who cannot take p.o. medication.

Patients with limited disease (taking MTX) will begin therapy with oral prednisone at doses ranging from 0.5 mg/kg to 1 mg/kg/day (not to exceed 80 mg/day), or the intravenous equivalent for patient who cannot take p.o. medication. Patients with limited disease will not be treated with methylprednisolone pulses.
4.2. Standard treatments

4.2.4. Corticosteroids

4.2.4.2. Tapering of corticosteroids

The goal of the prednisone taper is to achieve a cessation of prednisone use no later than 6 full months after randomization. Physicians will aim to taper the patients’ prednisone doses to 20 mg/day by the end of 2 full months. (If the starting dose is relatively low, e.g., 30 mg/day as opposed to 60, this goal will be reached earlier than 2 months). After achieving a dose of 20 mg/day, the prednisone will be tapered as follows:

- 20 mg/day x 2 weeks; then
- Reduce dose by 2.5 mg/week until reaching 10 mg/day; then
- Reduce dose by 1 mg/week until off.

Assuming that 2 months are required to taper the prednisone to 20 mg/day, the entire taper will require 6 months. In the event that an increase in corticosteroid dose is required by the patient’s condition (i.e., the occurrence of a disease flare during or after the taper), the patient may remain on the experimental treatment (see Management of disease flares; Section 6).
5. Concomitant medications

Because of the infectious and hematologic complications of using CYC or MTX in conjunction with corticosteroids, all patients in this trial will receive single-strength trimethoprim/sulfamethoxazole (T/S) once a day as prophylaxis against *Pneumocystis carinii* pneumonia. At the discretion of the study physician, double-strength T/S three times a week may be substituted for single-strength T/S daily. In the event of an allergy to sulfa medications, dapsone (100 mg p.o. q day) may be substituted for T/S after the measurement of a G6-PD level. If G6-PD levels preclude treatment with dapsone, prophylactic treatment for infections will be according to best medical judgment.

Patients on MTX will receive folic acid 1 mg p.o. q day. At the discretion of the study physician, patients treated with MTX who experience cytopenias, oral ulcers, or other complications presumed secondary to MTX may be treated with either:

- 2 mg of folic acid daily, or
- up to 5 mg/week of folinic acid (administered the day after MTX)

As prophylaxis against corticosteroid-induced osteoporosis, all patients will receive CaCO₃ (1 gram p.o. q day) and Vitamin D (400 I.U. p.o. q day). Other osteo-protective medications may be prescribed at the discretion of the study physician.
6. Management of disease flares

Flares of WG will be classified as limited or severe:

- **Limited flares** are defined as the new occurrence of one or more minor BVAS items. Limited flares are treated with increases in prednisone dose or an increase in MTX dose.

- **Severe flares** are defined as the new occurrence of one or more major BVAS items. Major items have a * on the BVAS scoring sheet. Severe flares are treated by increases in prednisone dose or CYC dose.

When appropriate for patient safety, patients who experience disease flares may remain on the assigned experimental treatment, provided that the standard treatment can be adjusted in a manner consistent with the protocol, as follows:

- Reinstitution of the same induction therapy used at trial entry. The patient will re-start one of the induction regimen described in Section 4.2, depending on the degree of severity of the flare.
- Return to a higher daily dose of corticosteroids (chosen at the discretion of the study physician). The increased dose of prednisone will be maintained for 28 days. After 28 days at the higher dose, the patient will resume the prednisone taper as outlined in Section 4.2.3.2.
- Patients initially treated for limited disease who suffer severe flares in the course of treatment may be converted from MTX to CYC. In the absence of contraindications, such a patient will be treated with daily CYC and an increased in prednisone dose (3-day pulse of methylprednisolone optional), as outlined in Sections 4.2.2 and 4.2.3.
- Patients with limited disease who suffer disease flares may be treated with an increase in the dose of MTX. If the MTX dose is increased, the patient will remain on the increased dose until he/she has been in remission for 12 months.

After the occurrence of two limited flares or after the occurrence of 1 severe and 1 limited flare, a patient may be maintained on a dose of prednisone not to exceed 10 mg/day (chosen at the discretion of the study physician) designed to maintain control of disease and minimize corticosteroid side-effects.

In the event of a flare, if the investigator believes that continuation of the experimental treatment is not in the patient’s best interests, the patient will stop receiving the experimental treatment and be treated according to best medical judgment. At the occurrence of a second severe disease flare during the trial, the experimental treatment will be stopped. Patients withdrawn from
the experimental treatment will continue to be evaluated according to the data collection schedule. Under most circumstances, the treatment assignments for the patients withdrawn from the experimental treatment will not be revealed until the common study closeout.
7. **Data collection plan**

7.1. **Data collection schedule**

Data are collected from all patients according to the schedule presented in Appendix E. This represents a data collection schedule, not a patient care schedule. Additional visits for adverse events or for other patient care needs should occur as necessary. However, except for information about adverse events and changes to experimental treatment, trial data will not be collected at these additional visits. Data collection forms for scheduled study visits include questions about treatment occurring between these visits. The study physician treating the patient will communicate with the patient’s local physician in the intervals between scheduled study visits.

Followup evaluations will be conducted at 6 weeks and 3 months following randomization, and every 3 months thereafter. All patients will be followed until death or until the common study closeout date, which will occur 12 months after randomization of the last patient. All patients, regardless of treatment assignment, will have the same data collection schedule. Patients receiving CYC will have complete blood counts (CBC) checked every 2 weeks. Patients receiving MTX will have CBC checked every month. These CBC may be collected by the patient’s local physician and faxed to the participating clinic.

7.2. **Medical history and physical examination**

Each patient will be evaluated for study eligibility prior to being randomized into the trial. Data to be collected include details of the patient’s WG diagnosis, treatment history, family history of rheumatic or immunologic disease, other medical illnesses, and concomitant medications. Detailed medical history data are collected at the baseline visit. General health information data are collected throughout the trial at every followup data collection visit. A physical examination is conducted at the baseline and all followup visits.

7.3. **Laboratory studies**

The following laboratory assessments are performed at every data collection visit:

- Serum chemistry: creatinine, blood urea nitrogen (BUN), electrolytes, albumin, ALT, and AST
- Complete blood counts (CBC)
- Westergren erythrocyte sedimentation rate (ESR)
- Urinalysis with microscopy

In addition to routine laboratory work, plasma, serum, whole blood and peripheral blood mononuclear cells will be collected for banking at every data collection visit. These procedures are described in the WGET Manual of Operations.
7.3. Laboratory studies

All women of childbearing potential will have a serum β-HCG test performed at baseline and at any time during followup if there is a suspicion of pregnancy.

Patients receiving CYC should have a complete blood count (CBC) performed every two weeks. Patients taking MTX should have CBC checked every month. These data will not be collected on study forms unless an adverse event is noted.

7.4. Chest radiographs

Radiographs of the chest will be performed at baseline and subsequently as indicated by the patient’s clinical condition.

7.5. Screening for Latent Tuberculosis Infection

All WGET patients should undergo a purified protein derivative (PPD) skin test for latent tuberculosis infection. Patients who have previously received the Bacille Calmette-Guérin (BCG) vaccination should still be tested with a PPD test, unless the BCG was administered within the past 3 years. Patients who have undergone PPD testing within 6 months are exempt. If patients do not wish to be screened for LTBI, they may refuse PPD testing following a discussion with the study physician.

Patients enrolled prior to the implementation of protocol version 3.0 should be screened with a PPD test at the next scheduled followup visit. All future patients who plan to enroll in WGET after the implementation of protocol version 3.0 should undergo PPD testing at the baseline visit. Guidelines for the screening of patients, the interpretation of PPD skin tests, and the management of patients following testing are provided in the WGET Manual of Operations.

7.6. Birmingham Vasculitis Activity Score for WG

The Birmingham Vasculitis Activity Score (BVAS) for WG will be assessed at every data collection visit. BVAS is described further in Section 8. BVAS is designed to document clinical features that are directly due to active WG. In assessing the BVAS score, the study physician must differentiate activity from damage. The list of items in BVAS includes clinical signs and symptoms, as well as information obtained from additional tests, e.g., urinalyses or sub-speciality consultations.
7.7. Birmingham Vasculitis Damage Index

The VDI is used to record organ damage that has occurred since the onset of WG. Damage is defined as the presence of non-healing scars and does not indicate current disease activity. Damage items in the VDI are often the direct result of previous disease activity. Birmingham Vasculitis Damage Index (VDI) will be assessed at baseline and, at all followup visits.

7.8. Patient global assessment of WG activity

Patients’ perception of WG activity is indicated on a 10-cm visual analogue scale. It is comparable to the physician global assessment on the BVAS form. Patient global assessment of disease activity will be collected at every data collection visit.

7.9. Quality of life

The SF-36 questionnaire is used to evaluate patients’ overall sense of well-being and quality of life at every data collection visit.

7.10. Adverse events

An adverse event (AE) is any untoward medical occurrence in a patient ever administered the experimental treatment (etanercept or placebo) that does not necessarily have a causal relationship with treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the experimental treatment. **ALL events that require hospitalizations or prolong an existing hospitalization, regardless of presumed association to WG or experimental treatment, should be reported as adverse events.** An adverse drug reaction (ADR) is any noxious and unintended response to the experimental treatment. “Response to” means that a causal relationship between the experimental treatment and the AE is at least reasonable possibility. All new ADRs will be reported on the Adverse Event Log. All infections, and serious injection site reactions will be recorded as well.

Adverse events will be graded according to the National Cancer Institute’s Toxicity Grading Scale. Adverse events not included in the Toxicity Grading Scale should be graded according to the following scale:

- **Grade 1:** mild, not requiring specialized treatment and causing no limitations of usual activities
- **Grade 2:** moderate, causing impairment of usual activities (e.g., outpatient pneumonia)
- **Grade 3:** severe, requiring vigorous therapeutic intervention; hospitalization usually required
- **Grade 4:** life-threatening, including immediate risk of death
- **Grade 5:** fatal
7.10. Adverse events

All serious adverse events (grade 3-5) or any event that required a hospitalization or prolonged an existing hospitalization must be reported to the Chairman’s Office (CO) on the Safety Report Form and faxed to the CO within 48 hours of clinic personnel learning of the event. The CO will be responsible for distributing safety reports to WGET participating sites, the NIAMS, the Immunex Corporation, the DSMB and the FDA, as appropriate. Summary reports of adverse events will be submitted to all IRBs monitoring the trial in conjunction with scheduled DSMB meetings.

The proper courses of action for reporting adverse events, toxicity grading scale, codes of infections, and other grading guidelines are listed in the WGET Manual of Operations.

7.11. Compliance

Compliance to the experimental treatment will be monitored via patient interview and vial counts. Patients will return all used vials of the experimental treatment at each study visit, and will be provided with a collection box to store used vials. Compliance with standard treatment and prophylactic regimens (CYC, MTX, prednisone, and others) will be monitored by patient interview.
8. Primary outcome measure

The primary outcome measure for this trial is remission achieved and maintained (sustained remission) in the two treatment groups. The Birmingham Vasculitis Activity Score (BVAS) for WG is the method of assessing disease activity and response to treatment. A sustained remission is defined as a minimum of 6 months of BVAS of 0 (i.e., 3 consecutive visits excluding the F01 visit).

BVAS is a clinical index of disease activity based on evidence of active WG in 9 separate organ systems. Disease features are scored in BVAS only if they are attributed to active WG (as opposed to damage). A BVAS score of 3 or greater, which is required for entry into the trial, indicates unequivocally active WG. BVAS has been validated as an index of vasculitis activity and employed in trials conducted by the European Community Systemic Vasculitis Clinical Trials Group. The BVAS Evaluation Form (see WGET Manual of Operations) is a one-page checklist of clinical features that reflect active WG. An Instructions’ Manual and Glossary for the use of BVAS, developed by the investigators, are included in the WGET Manual of Operations.
9. Secondary outcomes

9.1. Mortality

Time to death is measured from date of randomization. This measure will be censored at study closeout for patients still living.

9.2. Disease measures

- Mean BVAS over time
- Achievement and maintenance (for a minimum of 6 months) of a BVAS of ≤ 2
- End-stage renal disease
- Time from randomization to first BVAS of 0
- Time from sustained remission to first disease flare
- Number of severe flares (defined as a new occurrence of one or more major BVAS items)
- Number of limited flares (defined as a new occurrence of one or more minor BVAS items)
- Physician’s global assessment of WG activity
- Patient’s global assessment of WG activity
- Birmingham Vasculitis Damage Index

9.3. Adverse events

Occurrences of morbidity and abnormal laboratory measures will be collected. Rates of these events, including injection site reactions, infections, and hospitalizations will be calculated.

9.4. Quality of life

The SF-36 questionnaire is used to evaluate patients’ overall sense of well-being and quality of life. Change from baseline in patients’ quality of life will be evaluated.
10. Tertiary outcomes

Tertiary outcomes include laboratory tests, chest radiographs, and calculation of the quantities of standard treatment used.

10.1. Laboratory measures

- Change from baseline in the Westergren erythrocyte sedimentation rate
- Change from baseline in the serum level of C-reactive protein
- Change from baseline in ANCA titers as measured by immunofluorescence and enzyme-linked immunoassays

10.2. Treatment measures

- Completion of steroid taper regimen without disease flare
- For patients with severe disease at randomization, switch from CYC to MTX between 3 and 6 months without disease flare
- Cumulative doses of CYC and MTX
- Cumulative dose of prednisone
11. Biostatistics

11.1. Sample size calculations

The sample size of 180 patients (90 per treatment group) is based on pragmatic considerations of the availability of patients, recruitment histories of the participating clinics in other vasculitis studies and the 2.5-year enrollment period. It is projected that 180 patients will be enrolled by the end of 2002.

The primary outcome measure is achieving sustained remission any time during followup. Sustained remission is defined as remission for 6 months or more, i.e., at least 3 consecutive study visits with a BVAS score of 0. The minimum detectable relative improvement in remission rates between the treatment groups is 55%, assuming a total sample size of 180 patients, a 2-sided type I error of 0.05 using a chi-square test, 80% power, 40% of controls achieve sustained remission and 15% inflation of the sample size to account for loss to follow-up, non-compliance, and heterogeneity of effect associated with degrees of disease severity.\textsuperscript{16}

Table: Minimum detectable relative improvement in remission rates

<table>
<thead>
<tr>
<th>Sustained remission rate in controls</th>
<th>Minimum detectable relative improvement</th>
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</thead>
<tbody>
<tr>
<td>20%</td>
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<tr>
<td>30%</td>
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<td>40%</td>
<td>55%</td>
</tr>
<tr>
<td>50%</td>
<td>44%</td>
</tr>
</tbody>
</table>

11.2. Data analysis

General analysis principles include the following:

- The primary analysis will be performed according to patient’s original treatment assignment (intention-to-treat), regardless of the amount of the treatment administered
- All patients, including those who become ineligible after randomization and those who withdraw from the study, will be counted in their assigned treatment group
- All events following randomization will be analyzed
The primary statistical analysis will be a comparison of the rate of achieving sustained remissions in the etanercept and placebo groups. We hypothesize that patients assigned to etanercept will achieve a substantially higher rate of sustained remissions than those assigned to placebo.

Analyses that are both unadjusted and adjusted for explanatory factors such as demographics, clinic, newly-diagnosed versus previously-diagnosed disease, type of disease (limited versus severe), severity of renal involvement, and BVAS score at entry will be presented. Selection of adjustment covariates for the evaluation of treatment effect will be based on the method developed by Canner.\textsuperscript{9} Analyses of change over time in the individual BVAS components also will be analyzed. Subgroup analyses will compare those who were initially diagnosed as having limited versus those diagnosed with severe WG; those newly-diagnosed versus previously-diagnosed at trial entry, and those with a history of treatment refractoriness prior to trial entry. Other subgroup analyses will be performed (e.g., comparisons of outcomes of patients with and without clinical evidence of glomerulonephritis), but we acknowledge the exploratory nature of these analyses.

Other outcomes of interest include mortality, physicians global assessments, various morbidity measures (including the development of end-stage renal disease), time to 1° BVAS of 0, time to relapse for those patients achieving sustained remission, progression of disease (i.e., from limited to severe), adverse events, and toxicities. Cox proportional hazard models will be used to assess difference in mortality and other type of time-to-event outcomes.\textsuperscript{11,39} The effects of treatment on rates of flares, adverse events or hospitalizations will be examined with log-linear (Poisson) models.\textsuperscript{8} Generalized Estimating Equations will be used to assess repeated measures of change for continuous outcomes (e.g., SF-36 scores).\textsuperscript{41} We will use regression diagnostics such as goodness-of-fit tests and analyses of residuals and influential observations to assess the appropriateness of models.
12. Treatment effects and performance monitoring

12.1. Treatment effects monitoring

The WGET Data and Safety Monitoring Board (DSMB), comprised of independent experts in the fields of rheumatology, biostatistics, and clinical trials, will review the accumulating data with regard to safety and efficacy. In reviewing these data, the DSMB will be masked to treatment assignment. The voting members of the DSMB are not involved in the conduct of the trial and have no affiliation with the drug manufacturers. The members of the DSMB are listed in Appendix G.

The DSMB will meet at least 2 times a year to evaluate interim results. Additional meetings or conference calls of the DSMB will be scheduled as necessary. Summary reports of the DSMB deliberations will be submitted to all IRBs involved in the trial. Treatment assignments will be masked in those reports. Guidelines for early termination will be defined by the DSMB after consultation with investigators. These may include stochastic curtailment (conditional power) or group sequential guidelines (Type I error spending functions).22

12.2. Performance monitoring

Performance monitoring will include comparisons of enrollment, baseline variables, protocol deviations, and missing data by clinic. Clinic performance data will be presented at both the DSMB and Research Group meeting.
13. Regulatory and ethical considerations

13.1. Investigational New Drug (IND) regulations

The trial is conducted under a Sponsor-Investigator initiated Investigational New Drug (IND) number for etanercept (BB-IND 7960). John Stone, MD, MPH, the Study Chairman, holds the IND. The clinic directors, coordinators, and all study physicians will complete investigator statements (FDA form 1572) and submit them to the Coordinating Center (CC) prior to the start of the study. The 1572 forms and the WGET protocol will be submitted to the FDA by the CC before the start of the trial. Protocol amendments will also be submitted to both the FDA and NIAMS. The CC is also responsible for meeting reporting regulations of the FDA with regard to adverse events and annual reports.

13.2. IRB

This protocol will be submitted to the Institutional Review Boards (IRB) of participating centers for review and approval. Clinics that have obtained IRB approval for a previous version of the protocol will inform their IRB of changes to the protocol. Clinics may not recruit patients into the trial prior to approval of this protocol by their IRB. Protocol amendments and changes to the consent form will be submitted to the IRB in writing, and approval must be given before implementation. All serious adverse events related to WG or WG treatment, regardless of presumed relationship to the experimental treatment, will be submitted to the IRB overseeing the conduct of the trial.

All patients enrolled in the trial must sign and date an IRB-approved consent form and medical records release form before any study related procedures are undertaken. Study personnel will explain the study and answer all of the patient’s questions before asking the patient to sign and date the consent form.

13.3. Confidentiality of patient data

All patient data will be kept in a secure location. Names, social security numbers, addresses, and other such personal data will not be sent to the CC. Data collected from study evaluations and interviews will be identified only by study ID codes, which will be the patient ID number, medication ID number, and name code assigned at enrollment. Data without patient identifiers may be released to Immunex Corporation, the FDA, NIAMS, or other regulatory groups for monitoring purposes without further written consent of the patient. Clinically relevant information may be placed in the patient’s medical record. Release of data to any other persons or organizations will require additional written consent of the patient.
14. Biohazards

All personnel involved in collecting and handling biologic specimens should follow universal precaution procedures as currently recommended by the Centers for Disease Control and Prevention.
References

WGET Protocol (Version 3.0)

WGET Protocol (Version 3.0)

References

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A. Design schematic

180 patients

Clinic

Limited

Rz 1:1

Etanercept  Placebo

Severe

Rz 1:1

Etanercept  Placebo
B. Standard treatment algorithm for patients with severe WG

New Diagnosis or Flare

Start CYC / Pulse Steroids x 3 Days

Start Oral Daily Prednisone

After 1 Month: Begin Steroid Taper

3-6 months Treatment

No Remission

Limited Disease / Remission

Serum creatinine < 2 mg/dL

Begin MTX Therapy (D/C CYC)

If Remission x 12 Months on MTX, Begin MTX Taper by 2.5 mg/month

Continue experimental medication until common closing date of study

Serum creatinine >2 mg/dL

Begin AZA Therapy (D/C CYC)

If Remission x 12 Months on AZA, Begin AZA Taper by 25 mg/month

Remain on CYC
C. Standard treatment algorithm for patients with limited WG

New Diagnosis or Flare

Serious side effects due to MTX

Begin Daily Prednisone and Weekly MTX

After 1 Month: Begin Steroid Taper

If Remission x 12 Months, Begin MTX Taper by 2.5 mg/month

If Remission x 12 Months on AZA, Begin AZA Taper by 25 mg/month

Begin AZA Therapy (D/C MTX)

Continue experimental medication until common closing date of study
### D. Procedures and interviews required at scheduled visits

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*At baseline and during followup as clinically indicated
†Patient who will be returning to clinic more frequently than every 3 months (e.g., because of unstable disease or local standard of care) will receive med every six weeks
‡Patient taking CYC will have CBC checked every 2 weeks; patient taking MTX will have CBC checked every month
§At baseline for patients enrolled after the implementation of Protocol version 3.0. At next scheduled followup visit for WGET patients enrolled prior to the implementation of Protocol version 3.0.
## E. Data forms required at scheduled visits

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*Complete as needed
**Completed and faxed at the end of month
†Patient who will be returning to clinic more frequently than every 3 months (e.g., because of unstable disease or local standard of care) will receive med every six weeks
‡Required at missed visits
§For patients on experimental treatment
## F. List of clinical centers

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<thead>
<tr>
<th>WGET</th>
<th>Clinical Centers</th>
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<tbody>
<tr>
<td>BIMC</td>
<td>Beth Israel Medical Center New York, NY</td>
<td>Robert F. Spiera, MD</td>
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<tr>
<td>BUSM</td>
<td>Boston University School of Medicine Boston, MA</td>
<td>Peter A. Merkel, MD, MPH</td>
</tr>
<tr>
<td>CCF</td>
<td>Cleveland Clinic Foundation Cleveland, OH</td>
<td>Gary S. Hoffman, MD</td>
</tr>
<tr>
<td>DUKE</td>
<td>Duke University Durham, NC</td>
<td>E. William St. Clair, MD</td>
</tr>
<tr>
<td>JHU</td>
<td>Johns Hopkins University Baltimore, MD</td>
<td>John H. Stone, MD, MPH</td>
</tr>
<tr>
<td>MAYO</td>
<td>Mayo Clinic Rochester, MN</td>
<td>Ulrich Specks, MD</td>
</tr>
<tr>
<td>UCSF</td>
<td>University of California at San Francisco San Francisco, CA</td>
<td>John C. Davis, Jr, MD, MPH</td>
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<tr>
<td>UMMC</td>
<td>University of Michigan Medical Center Ann Arbor, MI</td>
<td>W. Joseph McCune, MD</td>
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### G. List of resource centers

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<thead>
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<th>WGET ID</th>
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<tr>
<td>CO</td>
<td>Department of Rheumatology</td>
<td>Chairman's Office</td>
<td>John H. Stone, MD, MPH</td>
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<td>The Johns Hopkins University</td>
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<td></td>
<td>Baltimore, MD</td>
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<tr>
<td>CC</td>
<td>The Center for Clinical Trials</td>
<td>Coordinating Center</td>
<td>Janet Holbrook, PhD, MPH</td>
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<td>Sponsor</td>
<td>Susana Sztein, MD</td>
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### H. Data and Safety Monitoring Board (DSMB)

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<tr>
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<td>Paul Canner, PhD</td>
<td>Maryland Medical Research Institute, Baltimore, MD</td>
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<tr>
<td>Doyt Conn, MD</td>
<td>Emory University, Atlanta, GA</td>
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<tr>
<td>Jack Klippel, MD</td>
<td>Arthritis Foundation, Washington, DC</td>
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<tr>
<td>Richard Landis, PhD</td>
<td>University of Pennsylvania, Philadelphia, PA</td>
</tr>
<tr>
<td>Barbara White, MD</td>
<td>University of Maryland, Baltimore, MD</td>
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I. Prototype WGET Consent form

Prototype Consent form follows
The Wegener’s Granulomatosis Etanercept Trial (WGET)  
Prototype Consent form

INTRODUCTION:

This is a research study to evaluate additional treatments in Wegener’s Granulomatosis. This study is being performed by the Wegener’s Granulomatosis Etanercept (WGET) group. Johns Hopkins University (JHU) is one of eight centers in the United States participating in this study. Taking part in this study is voluntary. You may ask any questions you have about this study with our staff members.

WG is an inflammatory disease of blood vessels. Its cause is unknown. The blood vessels that become involved may be anywhere in the body. Most often including the vessels that supply blood to the kidneys, lungs, and upper respiratory tract (nose, sinuses). In WG, blood vessels often become inflamed, narrowed, and closed off. Sometimes blood vessels fail to carry enough blood to vital organs. This may cause kidney failure, shortness of breath, coughing up of blood, hearing loss, and damage to the eyes. There may be many other complications, depending on which organs are involved.

We know that the symptoms of WG usually get better when treated with medicines that calm down the immune system. These medicines include steroids (prednisone), methotrexate, and cyclophosphamide. Unfortunately, these drugs are associated with many side-effects, described below. Treatment of WG starts with high doses of these medicines to provide quick relief. Next, the doses are lowered to the lowest amounts capable of controlling the disease. In some cases the medicines can be stopped without a return of the disease. In other cases, the disease comes back, requiring use of the medicines again.

PURPOSE:

This is a research study to determine whether treatment with standard medications for WG plus another medication called Enbrel™ (generic name: etanercept) can result in better control of your/your child’s illness. Enbrel™ is a medicine that is injected under the skin twice a week. It is designed to work by inhibiting the function of tumor necrosis factor. This is a substance that is known to participate in the inflammation associated with WG.

Enbrel™ is approved by the United States Food and Drug Administration (FDA) for use in the treatment of rheumatoid arthritis. Enbrel™ has been shown to be effective in treating rheumatoid arthritis (another disease associated with inflammation). We would like to find out if Enbrel™ will be effective in treating WG. The use of Enbrel™ for the treatment of WG is investigational, but this
I. Prototype WGET consent form

investigational use has been approved by the FDA. To do that, we need to compare patients treated in the usual way (with standard treatment) to those treated with standard treatment plus Enbrel™.

PROCEDURES:

If you/your child agree(s) to join the study, the following will be done at the time you/your child enter(s) the study:

- A medical history and physical examination
- Blood tests to assess how active your disease is, as well as how well your/your child’s liver, kidneys, and other organs are working (this will require about 8 teaspoons of blood)
- A urine test
- A skin test for tuberculosis
- A chest X-ray
- If you/your child are/is a woman who is able to have children, a pregnancy test will be done
- You/your child will fill out a survey about the impact of your/your child’s disease on your/your child’s quality of life (this will take approximately 10 minutes)

Because patients treated for WG have suppressed immune systems, an infection called tuberculosis (TB) is a concern. This is why we would like to perform a skin test for TB. If the test is positive, further tests such as a chest x-ray may be required. If TB is confirmed, your/your child’s doctor will prescribe medications. You/your child may still participate in this trial if you/your child refuse(s) to have the skin test for TB.

The blood and urine tests will be repeated at regular intervals throughout the study. Some of the blood tests (not drawn more than every 6 weeks) and urine tests will be used for studies related to the cause, outlook, and how the disease works (WG). Some of your/your child’s blood will be stored for future research studies related to WG. These studies may involve testing for the presence of genes (DNA) and studies of blood factors (e.g., antibodies or novel inflammatory proteins). These may influence the risk of getting WG the risk of having a severe form of the disease, and the chance of responding to treatment.

You may still participate in this trial without having extra blood drawn and stored for research purposes. Please read the following statements, and mark and initial the box of your choice:

_______ (subject initials) “I permit my blood samples to be collected, stored, and used in future research studies related to WG”.

_______ (subject initials) “I do not permit my blood samples to be collected, stored, and used in future research studies related to WG”.

WGET Protocol Prot3.0 Manall.7
9:30am Friday, 8 Feb 02/pts
I. Prototype WGET consent form

Treatment Assignment

If you/your child agree(s) to participate, you/your child will be assigned by “chance” (like flipping a coin) to either: 1) standard treatment plus a placebo, or 2) standard treatment plus Enbrel™. A placebo is a liquid that looks like the Enbrel™ liquid but has no Enbrel™ in it. Both Enbrel™ and the placebo are given by injection with a small needle under the skin, twice a week. You/your child will not know which treatment you/your child are/is taking. Following your/your child’s entry visit, you/your child will have a study visit at one six week interval, and then every 3 months from time of entry (entry, 6 weeks, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, etc.) until the end of the trial. The trial will end after the 180th patient has been in the trial for 1 full year.

Each appointment will take approximately 1-2 hours of time. This appointment schedule is typical for a patient with WG whether or not the patient is enrolled in a study. If your/your child’s medical condition requires additional visits with a doctor, other visits will be scheduled as necessary. During all of these visits a doctor will examine you/your child. Also at each study visit about 8 teaspoons of blood will be taken from a vein in your/your child’s arm. This would be commonly done even if you/your child were not in a research study. You/your child will also give urine specimens at each visit.

Your/your child’s physician will not know whether you/your child are/is taking Enbrel™ or placebo. The code that tells which patients are receiving Enbrel™ and which are receiving placebo will be kept by the study coordinating center. This code will be kept private until the end of the study, unless it is necessary to break the code in the interest of your/your child’s safety. Depending on your/your child’s symptoms and the lab results, the doses of some of the medications used in the study (all except for Enbrel™ or the placebo, which will remain the same unless they need to be stopped entirely) may be changed by your/your child’s physician. Once you/your child have/has clearly responded to treatment, some of your/your child’s medicines will be tapered over a period of months. This is expected to occur within several weeks in both groups.

RISKS / DISCOMFORTS:

Risks Associated With Standard Medicines Used To Treat WG

Long-term use of prednisone, methotrexate, and cyclophosphamide may be associated with significant side effects. These include: low blood cell counts; infections; weight gain; fluid retention; puffiness of the face and other body areas; more easily damaged skin; bruising; loss of muscle and bone strength; increased risk of broken bones; mood changes; difficulty sleeping; cataracts (clouding of the lenses of the eyes); risk of high blood pressure and diabetes; cancer of the bladder, bone marrow, or other organs; and damage to the liver or lungs; or death. All of these can be serious complications.
Standard therapies used to treat WG have significant potential side effects. For that reason, you/your child will be asked to take medications to prevent the occurrence of as many of these side effects as possible. These preventive medicines include folic acid (a vitamin) and trimethoprim-sulfamethoxazole (TMP/SMZ), a sulfa antibiotic that is used to prevent a certain type of pneumonia. If you/your child are allergic to sulfa medicines, you/your child may take a medicine called dapsone instead.

If you/your child are taking methotrexate as part of your/your child’s treatment for WG, we strongly discourage the drinking of alcohol. In order to participate in this trial, you/your child must be willing to limit your/your child’s intake of alcohol to 1 alcoholic drink or less per week.

**Risks Associated With The Use Of Enbrel™**

In studies comparing Enbrel™ to placebo, side effects that occurred more frequently in Enbrel™-treated patients were mild reactions at the site of injection under the skin. Injection site reactions consisted of redness, pain, swelling, or itching. In a small percentage of patients treated with placebo, injection site reactions have also occurred, consisting of redness, pain, swelling, or itching. Allergic reactions have also been reported rarely in patients treated with Enbrel™.

Enbrel™ is a protein based on a substance that occurs naturally in humans. It does not allow another substance in the body (TNF) to be present. In theory, a decrease in TNF may result in cancer, autoimmunity (a condition in which the body reacts with its own tissue), or infection. To date, the incidence of cancer in patients receiving etanercept has been found to be the same as that of untreated people. Results of clinical trials do not show that Enbrel™ causes autoimmune diseases or that it increases infections.

It is still possible that Enbrel™ may make infections worse and could result in life-threatening complications. The infections may occur in any body system. Serious infections, including deaths from infection, have been reported with the use of etanercept. Many of these infections occurred in patients with diseases that tend to weaken the body’s ability to fight infection. In some patients, very low blood cell counts have been reported. If you/your child develop(s) signs and symptoms of a significant infection or persistent fever, bruising, bleeding, or very pale skin, you/your child should contact your/your child’s physician immediately.

Rare neurologic events, including multiple sclerosis, have been reported. If you/your child are found to have multiple sclerosis, or develop weakness or visual disturbances, notify your/your child’s physician.

Other serious conditions that have been reported in patients receiving etanercept include: heart problems, such as heart failure and heart arrest; high and low blood pressure; circulation, bleeding and clotting problems; delayed healing; stroke; shortness of breath; digestive system disorders (including intestinal perforation); kidney problems; back or joint pain; diabetes; weakness; and rash. These serious conditions were rare and it is unclear whether or not etanercept was the cause.
A small number of people receiving Enbrel™ have formed antibodies against Enbrel™. Your/your child’s body naturally makes antibodies as a way to protect itself from unknown material in the body. These antibodies do not appear to be active in blocking the effect of Enbrel™. Any further effects of an individual having antibodies to Enbrel™ are not known.

In patients with Crohn’s disease, a chronic inflammatory condition of the gastrointestinal tract, serious sudden intestinal blockage and dizziness have been reported.

All men and all women who are able to have children must practice an adequate method of birth control while participating in this trial and for 3 months after stopping the experimental treatment. Adequate methods of birth control include: sexual abstinence (not having sex), oral contraceptives (“birth control pills”) or other hormone-based method, the using both a condom and a diaphragm, using both a diaphragm and spermicide, tubal ligation (for women), and vasectomy (for men). Inadequate methods include: the rhythm method, withdrawal, condoms (alone), diaphragm (alone), and an intra-uterine device (IUD).

Pregnant or nursing women, women of childbearing potential, and fertile men not using an adequate method of birth control are not permitted to participate in this study. The risks of the study drug to an unconceived, unborn, or newborn child are not known. If you/your child are/is a woman who could become pregnant, you/your child will agree to notify your/your child’s physician immediately if you/your child suspect(s) or know(s) you/your child are/is pregnant while on the study. If you/your child are/is still receiving study drug, you/your child will discontinue the experimental medication, but will continue to be followed as a patient in the trial. There may be other unknown side effects that could occur during the time you/your child participate(s) in the study or years after receiving the drug. If there are any important new findings that may affect your/your child’s willingness to continue in the study, you will be notified.

In order to minimize or avoid the risks and hazards associated with the use of Enbrel™, the following will be performed:

1. Study medications will be given under close supervision of you/your child’s study doctor, who will perform frequent evaluations.
2. In order to safeguard against blood, liver, kidney or other organ damage possibly caused by any of the study medications, blood and urine tests will be performed regularly.
3. If dangerous or otherwise intolerable side-effects occur, the study medication will be stopped.
4. You/your child should report any unusual reactions promptly to your/your child’s study doctor.
Other Possible Risks Associated With Participating In This Study
Blood tests or administration of drug by injection under the skin can cause symptoms like local pain, bleeding, bruising, and, rarely, infection. The radiation exposure you/your child will receive from a normal chest X-ray is equivalent to an exposure of 0.007 rem to your/your child’s whole body. There is radiation that occurs in nature (cosmic radiation, radon, etc.), which produces whole body radiation exposures of about 0.3 rem per year. People who work with radiation for their job are permitted to receive whole body exposures of 5 rems per year.

BENEFITS:

It cannot be guaranteed that you/your child will receive any benefits from this study. Benefits to others may include knowing the safety and effectiveness of Enbrel™ in the treatment of WG. There is no guarantee that the study medication will be provided beyond the 12 to 42 month study period.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY:

If you/your child are/is not eligible or decline to participate in this study, you/your child will receive standard treatment for WG. Your signature below indicates that the doctor identified at the end of this form or one of his or her staff members has discussed with you/your child other ways your/your child’s WG might be treated should you/your child decide not to join this particular study.

Right To Refuse Or Withdraw
The choice to enter or not enter this study is yours/your child’s. You/your child are/is in a position to decide if you/your child understand(s) both what the doctor has explained and what you/your child have/has read about the study. If you/your child decide(s) not to participate, other choices are available to you/your child without prejudice. If you/your child begin(s) the study, you/your child have/has the right to withdraw at any time. If you/your child withdraw(s), you/your child will be offered other care according to your/your child’s condition. In either case, there will be no penalty or loss of benefits to which you/your child deserve.

Reasons For Withdrawal From The Study Without Your/Your Child’s Consent
If any of the following things happen, you/your child will be withdrawn from the study without your/your child’s consent:

a) The investigator decides that continuing in the study would be harmful to you/your child;
b) You/your child need(s) a medication not allowed on this study;
c) You/your child fail(s) to keep appointments or take medications as instructed;
d) You/your child have/has a serious adverse reaction to the study medications;
e) You/your child become(s) pregnant;
f) The study is cancelled by the National Institutes of Health, the Food and Drug Administration, or Immunex;
I. Prototype WGET consent form

Discovery of alcohol abuse if you/your child are/is taking methotrexate as part of your/your child’s treatment for WG.

Costs Or Payment To You/Your child
There is no cost to you/your child for Enbrelä or the placebo medications. Also, there is no cost to you for laboratory tests or examinations that are not standard in the treatment of WG. The medical costs of clinic visits, examinations, and laboratory tests that are standard in the treatment of WG will be charged to you and your health insurance company. You/your child will be reimbursed $25.00 for each regularly scheduled trial visit for money you spend to participate in this study (parking, gas, etc.).

CONFIDENTIALITY:

We are collecting data for the purpose of this study. We will keep the data at your/your child’s clinic and at the study coordinating center in Baltimore, Maryland. Your/your child’s research records will be kept confidential to the extent permitted by the law. You/your child will be identified by a study number. Personal information from your/your child’s records will not be released without your/your child’s written permission. Unless required by law, only the team of investigators involved in this study, the Institutional Review Boards of universities participating in the study, the National Institutes of Health or its representatives, the Data and Safety Monitoring Board, and the United States Food and Drug Administration will have access to your/your child’s study and associated medical records. The pharmaceutical company providing the medication will have access to your/your child’s study data sets that do not include personal identifiers. Medical information from the study will be made available to your/your child’s physician unless you/your child specify otherwise. If a health condition is detected during the study, you/your child will be told about it and the information will be given to your/your child’s doctor or clinic. A Safety Officer has been named to monitor the safety of this clinical trial. He will review data routinely to assess safety concerns. Your/your child’s records from this study will be retained for seven years. Your/your child’s identity will not be revealed in any publication or release of results. This study is authorized by Privacy Act 42 United States Code 241.

If you/your child have/has any questions about any part of the study or your/your child’s rights as a volunteer, a WGET staff person will be on hand to answer them before you/your child sign(s) this consent form. If you/your child have/has any questions at any time you/your child may call Dr. John Stone at 410-614-4905, or any of the staff persons listed at the beginning of this document. Before you/your child sign(s) this form, please ask any questions on any part of this study that is unclear to you/your child.
NEW FINDINGS

You/your child will be told of any new information learned during the course of the study that might cause you/your child’s mind about staying in the study. At the end of the study, you/your child will be told when study results may be available and how to learn about them.

QUESTIONS YOU MAY HAVE ABOUT THE RESEARCH STUDY:

This consent form explains the research study. Please read it carefully. Ask questions about anything you do not understand. If you do not have questions now, you may ask later. During the study, you will be told any new facts that could affect whether you want to stay in the study. If the study relates to a health problem you have, we will explain what other treatment could be given outside the research. You should understand those options before you sign this form. If you have questions you should call the principal investigator John H. Stone, M.D., M.P.H. at 410-614-5899.

PRIVACY INFORMATION:

We will keep the study information private to the extent possible by law. However, State law requires us to report certain contagious diseases or if we find information about child abuse. Also, under certain conditions, people responsible for making sure that the research is done properly may review your study records. This might include people from Johns Hopkins, the National Institutes of Health, the Food and Drug Administration, or the sponsoring company (if any). All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study, unless you give permission.

IN CASE OF INJURY:

If you are injured as a result of being in the study, or think you have not been treated fairly, please contact Dr. Stone at 410-614-5899. The services at the Johns Hopkins Hospital or the Johns Hopkins Bayview Medical Center will be open to you in case of any such injury. However, the Johns Hopkins University, the Johns Hopkins Hospital, the Johns Hopkins Bayview Medical Center, Immunex, and the Federal Government do not have a program to pay you if you are hurt or have other bad results which are not the fault of the study doctors.

You and your insurance company will be responsible for payment of any treatment or hospitalization you require if you are injured as a result of being in the study. It is up to you to check with your insurance company before you start this study to find out what your insurance company would pay for.
QUESTIONS ABOUT YOUR RIGHTS AS A RESEARCH SUBJECT:

If you have any questions about your rights as a subject in a research project, you should call the Joint Committee on Clinical Investigation at (410) 955-3008, or the Johns Hopkins Bayview Medical Center Institutional Review Board for Human Research (410) 550-1853 to receive help or advice.

JOINING OF YOUR OWN FREE WILL (Volunteering for the study):

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join the study, you will not be penalized or lose any benefits to which you are otherwise entitled.
WHAT YOUR SIGNATURE MEANS:

Your signature below means that you understand the information given to you about the study and in this consent form. If you sign the form it means that you agree to join the study.

WE WILL GIVE YOU A COPY OF THIS CONSENT FORM.

STUDY APPROVED FOR ENROLLMENT OF: __Adults Only __Adults and Children __Children only

NOT VALID WITHOUT THE COMMITTEE OR IRB STAMP OF CERTIFICATION

PROTOCOL WILL EXPIRE: ______________ (Date)

Subject's signature (including children, when applicable) Date

Signature of Parent or Legal Guardian (when applicable) Date

Surrogate Signature for Subjects not Competent to Give Consent Date

Relationship of Surrogate to Subject: __________________________

Signature of Investigator or IRB/JCCI Approved Designee Date

Witness to Consent Procedures(Optional unless subject is illiterate, or unable to sign) Date

NOTE: A COPY OF THE SIGNED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PATIENT’S RECORD
J. Prototype Assent form for Minors

Prototype Assent form follows
WGET Assent form for Minors
(patients < 18 years old)

This assent statement is for patients who are minors (under 18 years of age). A parent or guardian of the patient should read and sign the Consent Form before the patient is enrolled.

You have a disease called Wegener’s granulomatosis. Your doctor can give you different drugs for it. We are doing a study to compare the effectiveness of a new drug called Enbrel to the standard way of treating your disease. If you agree to be in this study, you will be assigned to one of two treatments: the standard treatment plus Enbrel, or the standard treatment plus a “placebo” (or fake medicine). The treatment you get will be picked by chance, like flipping a coin.

Taking Enbrel or the placebo requires a shot twice a week. If you have a bad reaction to the shots or if the treatment you are on does not seem to be working, your treatment will be changed. You and your doctor will decide what new treatment is best for you.

Standard treatments for Wegener’s granulomatosis include medicines like prednisone, methotrexate, and cyclophosphamide. These drugs sometimes have serious complications, like infections, weight gain, risk of some kinds of cancer, puffiness of the face and other body areas, and changes in moods.

If your Wegener’s granulomatosis gets worse while you are in the study, you and your doctor will decide what to do. You may keep taking the same drugs or change to another drug. If you have a bad reaction to the drug, your doctor will treat the problem. Your doctor also may change you to another drug.

Some patients need to stay on some type of treatment for Wegener’s granulomatosis for many years. Others are able to stop treatments after a couple of years, but the disease often comes back when treatments are stopped. In this study, you will be treated for as little as a year or as much as three and a half years, depending on when you start the study. If your disease goes away while you are on the study, the standard medicines that you are taking will be decreased or stopped. However, if your Wegener’s granulomatosis becomes active again, you will need to start taking the standard medicines again.

You will need to come to the clinic for checkups at least every six weeks at first (and then every three months after the third visit). You may need to come back to the clinic for check-ups more often than this if your Wegener’s granulomatosis is not under good control or if other aspects of your medical condition require more frequent care. At these checkups, we will ask you questions about your health and the medicines you are taking. At the regularly scheduled visits, we will draw blood and perform tests of your urine to make sure your disease is not getting worse. You will also need to have blood drawn more frequently to make sure that you are not having bad side-effects of the medicines. At the regularly-scheduled visits, we will also save blood samples for the purpose of doing research in Wegener’s granulomatosis. In all, the blood tests will require about 8 teaspoons of blood.
Using a vein to take blood samples or to give treatment has some risks. The risks include pain, and infection. There may be redness, swelling, and bruises where the needle is put through the skin.

All drugs have side effects. You and your doctor must weigh the risks of side effects against the possible benefits of taking the drug.

Sometimes Enbrel causes side-effects. The most common side-effect is redness and tenderness at the site where the medication is injected. This problem occurs only occasionally in some patients. Enbrel may also increase the risk of some kinds of infections. If your doctor believes that you have an infection, the doctor will stop your Enbrel at least temporarily.

In studies comparing Enbrel™ to placebo, side effects that occurred more frequently in Enbrel™-treated patients were mild reactions at the site of injection under the skin. Injection site reactions consisted of redness, pain, swelling, or itching. In a small percentage of patients treated with placebo, injection site reactions have also occurred, consisting of redness, pain, swelling, or itching. Allergic reactions have also been reported rarely in patients treated with Enbrel™.

Some of the standard medicines used to treat Wegener’s granulomatosis have caused cancer in humans. (For this reason, your doctor tries to limit the amount of time that you take these standard medicines). No one knows if Enbrel causes cancer in humans or not. Both the standard medicines and Enbrel may also affect eggs, sperm, or an unborn baby. If you have sex, you should practice safe sex. If a girl or woman gets pregnant, the Enbrel or placebo will be stopped, and she and her doctor will decide if her the standard medicines should be changed. Girls and women will take a pregnancy test (a blood test) before starting treatment in this study.

You may benefit from the care you will receive. We will examine you regularly and check tests to help make sure that your disease is improving. The drugs we use may stop the Wegener’s granulomatosis from getting worse. Also, you may help to improve treatments for other people with Wegener’s granulomatosis.

You may decide not to be in this study. You also may get out of the study at any time. At any time you may ask the doctors or clinic staff at this center questions. They include Dr.______________________ or ______________________. If you decide not to be in the study, it will not affect your medical care. No one involved in the study will be angry with you.
We would like you to discuss this study with others before you decide to take part in it. If you want, you can get more details about the study from the Consent Statement.

Signature of patient                               __/__/       Clinic ID code: __________________
Date                                         Patient ID#: __________________

Patient name code: __________________

FOR WGET STAFF ONLY:
I have reviewed the contents of the Informed Consent Statement with ______________________ at his or her level of understanding. I feel he or she understands the study requirements.

Signature of WGET staff member                             __/__/       Date
K. Glossary of abbreviations and definitions

**Active disease** – Any BVAS item (major or minor) is present. For trial inclusion, the patient’s BVAS score must be 3 or greater (or have been 3 or greater within 28 days of randomization). Each major item on the BVAS evaluation form is scored 3 points. Each minor item is scored 1 point. (Note: In determining the degree of disease activity, the investigator will distinguish between active vasculitis (new/worse BVAS items as opposed to persistent items) and permanent organ damage caused by previously active vasculitis.)

**ACR** – American College of Rheumatology

**ANCA** – Antineutrophil cytoplasmic antibody

**AZA** – Azathioprine

**BVAS** – Birmingham Vasculitis Activity Score – an index of vasculitis activity. It is designed to document clinical features that are directly due to active WG. The instrument separates the features that represent new or worse disease activity from those that represent persistent activity.

**CYC** – Cyclophosphamide

**DSMB** – Data and Safety Monitoring Board

**FDA** – Food and Drug Administration

**HIV** – Human immunodeficiency virus

**Limited flare** – New occurrence of one or more minor BVAS items. Generally, such flares are treated with increases in prednisone dose or an increase in MTX dose.

**Limited WG** – Occurring in a patient who meets the modified American College of Rheumatology (ACR) criteria for a diagnosis of Wegener’s Granulomatosis but who does not have disease that poses an immediate threat to either a critical individual organ or to the patient’s life. Specifically, this means that:

- The patient has no red blood cell casts in the urine.
- If hematuria (but no +RBC casts) is present, the serum creatinine must be \(< 1.4\) and there must be evidence of no rise of creatinine more than 25% above the patient’s baseline.
Appendix J. Glossary of abbreviations and definitions

- Pulmonary involvement must be circumscribed, such that the room air pO₂ is > 70 mmHg or the room air O₂ saturation by pulse oximetry is > 92%. Pulmonary hemorrhage may be treated as limited disease provided there is no evidence of progression of the process. In the absence of data on progression, pulmonary hemorrhage may be treated as severe disease at the discretion of the physician.

- No disease may exist within any other critical organ (e.g., the gastrointestinal tract, eyes, central nervous system) that, without the immediate institution of maximal therapy (i.e., pulse methylprednisolone and daily oral cyclophosphamide), threatens the function of that organ and/or the patient’s life.

LTBI – Latent tuberculosis infection – positive PPD test

MTX – Methotrexate

Newly-diagnosed patient – A patient on his/her first treatment course of corticosteroids and/or a cytotoxic agent for WG, with no history of increase in immunosuppressive therapy prior to WGET entry

NIAMS – National Institute of Arthritis, Musculoskeletal and Skin Diseases

NIH – National Institutes of Health

Persistent disease – For the purpose of scoring BVAS, persistent disease is defined as the presence of ongoing disease activity that was present at the previous trial evaluation (i.e., not new or worse activity).

PPD – Purified protein derivative skin test for latent tuberculosis infection.

RA – Rheumatoid arthritis

Refractory patient – A patient with a history of immunosuppressive therapy (corticosteroids and/or a cytotoxic agent) prior to the initiation of treatment for the WG activity and made the patient eligible for WGET

Remission – Patients will be considered to be in remission when their BVAS score is 0.

Severe flare – New occurrence of one or more majorBVAS items. (Major items have a * on the BVAS scoring sheet). Generally, such flares are treated by increases in prednisone dose or CYC dose.

Severe WG – Any patient with Wegener’s granulomatosis whose disease is not classifiable as limited has severe disease, by definition.
WGET Protocol (Version 3.0)

Appendices

Appendix J. Glossary of abbreviations and definitions

TNF – Tumor necrosis factor

T/S – Trimethoprim - sulfamethoxazole

WG – Wegener’s Granulomatosis

WGET – Wegener’s Granulomatosis Etanercept Trial