ECSYSVASTRIAL PROTOCOL

Treatment of refractory Systemic Vasculitis with Anti-Thymocyte-Immunoglobulin (ATG)

SOLUTION

Investigators: European Community Concerted Action Group for the Study of Therapeutic Trials in Systemic Vasculitis (ECSYSVASTRIAL)

Subcommittee for new drugs of the European Vasculitis Study group:
Daniel Abramowicz (Brussels), Konrad Andrassy (Heidelberg), Kirsten de Groot (Lübeck), Fokko van der Woude (Mannheim), Martin Lockwood (Cambridge), Francois Lothé (Bobigny/Paris), Conleth Feighery (Dublin), Carl Siegert (Leiden), John Boletis (Athens), Rainer Nowack (Mannheim), Annette Bruchfeld (Stockholm)

Co-ordination:
Rainer Nowack, Luis F. Flores Suárez
and Fokko J. van der Woude
Vth Medical Clinic
Klinikum Mannheim
Faculty of Medicine of the
University of Heidelberg
Theodor-Kutzer-Ufer 1-3
D-68135 Mannheim
Tel. 0621/383 2340
Fax.0621/383 3804
E-mail: woude@rumms.uni-mannheim.de

Contents

Summary:
Systemic vasculitides predominantly affect small blood vessels with a heterogeneous clinical presentation. Their standard treatment with corticosteroids and cyclophosphamide is usually effective at controlling active disease. However, a small group of patients suffers from persistent disease, refractory to standard drugs like cyclophosphamide or azathioprin and corticosteroids. In other patients initiation or continuation of these standard drugs is contraindicated due to intolerable side-effects.
No well established therapy is available for such patients. They may suffer severe organ damage due to progressive disease, or may die. In pilot studies antibodies against T-lymphocytes (ATG) have shown promising results in such refractory cases. This study is an open, multicenter, study to investigate the efficacy and side effects of ATG-treatment in patients with systemic vasculitis, who cannot receive standard therapy.

1. Introduction

The ECSYSVASTRIAL study group was convened in January 1994 under the European Community (EC) BIOMED 1 concerted action programme to co-ordinate therapeutic trials in systemic vasculitides (SV) in particular Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA). This was itself a development from an existing EC/BCR study group concerned with the design and standardisation of solid phase assays for determination of anti-neutrophil cytoplasmic antibodies (ANCA, autoantibodies prevalent in systemic vasculitides) brought together in 1991. The aims of the ECSYSVASTRIAL study group include the design and standardisation of disease scoring and data collection methodology, the design and facilitation of therapeutic trials and the harmonisation and improvement of the treatment of these disorders within the EC. These subtasks are carried out by subcommittees formed by members of the ECSYSVASTRIAL including the **subcommittee for new drugs**, who is responsible for the present protocol.

An approach to the treatment of SV based on the extent and severity of disease has been developed by the ECSYSVASTRIAL study group. Four basic treatment protocols have been designed for WG and MP:

1. early systemic WG or MPA without overt renal involvement (NORAM)
2. WG, MPA or renal-limited vasculitis (RLV) with slight to moderate renal involvement or other threatened vital organ function (CYCAZAREM)
3. WG, MPA or RLV with severe renal involvement (MEPEX)
4. **SV cases refractory to standard treatment (SOLUTION, this protocol)**

The ECSYSVASTRIAL activities are continued with four new treatment protocols under the AVERT (ANCA-associated Vasculitis European Randomised Trials) project supported by the European Community (EC) BIOMED-2 concerted action programme. The study group responsible for both projects is the "European Vasculitis Study Group" (EUVAS).

The EUVAS activities are co-ordinated by Niels Rasmussen, Department of Otolaryngology, Rigshospitalet, 2100 Copenhagen, Denmark.

2. Systemic vasculitis (SV) and its treatment

Systemic vasculitides (SV) are diseases of unknown etiology, which have been diagnosed increasingly in recent years because of new diagnostic techniques and growing awareness among physicians. Their pathogenesis has an autoimmune basis but is not completely understood. SV may be limited to few organs in early stages, but subsequently tend to generalize. The following entities belong to SV: Wegener´s Granulomatosis (WG), Microscopic Polyangiitis (MP), and renal limited disease (RLV). Disease definitions are given in the appendix.

Untreated SV has a high mortality within few months after onset of disease. The standard treatment to induce remission of SV is a combination of cyclophosphamide

(CYC) and corticosteroids (OCS) (1). The treatment with OCS alone does not lead to long-term remissions. How long CYC should be maintained after remission is under discussion. The role for other, less toxic drugs in maintenance therapy of SV is currently investigated, as well as their efficacy in limited forms of SV, e.g. methotrexate for WG limited to the upper respiratory tract.

3. Treatment of refractory disease

Standard induction therapy fails to induce remission in about 10% of patients. Relapses occur in 40% of patients within 24 months after successful induction of remission. Relapses indicate a poorer long-term prognosis. The usual therapeutic management of such cases is prolonged administration of CYC, or readministration of CYC. In frequent relapsers this will often lead to high cumulative doses of CYC. The risk for severe side-effects of CYC, e.g. malignancies and bone-marrow toxicity, increases dramatically in patients with a cumulative dose of CYC higher than 100 g. There is a definite need to replace CYC in these refractory cases. Few patients have been reported to have responded to Cyclosporin A (2), intravenous immunoglobulins (3) or humanized antibodies against lymphocyte antigens (CAMPATH) (4).

However, the number of reported patients is low, and these drugs have never been studied in controlled trials. Polyclonal anti-T-lymphocyte globulin (ATG) has been reported to be effective in 4/5 patients with severe, refractory SV (5). In contrast to CAMPATH, which could only be used by few centers with the necessary expertise to manage the side-effects, renal physicians are well acquainted with the usage of ATG for prophylaxis or treatment of renal-transplant rejections. ATG could therefore become a wider-spread therapeutic approach for refractory SV.

4. Study medication: ATG

The central role that thymus-derived lymphocytes play for the autoantigen recognition and antibody response in autoimmune diseases is the basis for the usage of lymphocytotoxic sera in SV. Activated T-lymphocytes are usually found in sites of vasculitic inflammation. ATG is directed against surface-antigens of activated lymphocytes and results in lymphocyte-depletion and thereby modifies autoimmunologically triggered inflammation. Polyclonal ATG and monoclonal antibodies against lymphocyte-antigens have been effectively used for prophylaxis and treatment of transplant-rejections. ATG has been successfully administered to patients with refractory systemic sclerosis (6), systemic lupus erythematodes, autoimmune hemolytic anemia, rheumatoid arthritis (7) and SV (5). The overall number of treated patients is small, but in a considerable number of patients a single course of ATG led to significant, long-lasting disease remissions. However, not all patients did benefit from ATG -treatment. In the light of the spectacular success of ATG in some patients, a controlled trial is extremely warranted and it is important to find criteria which help to identify patients who are likely to respond to ATG-treatment.

Acute side-effects of ATG are well known from the experience with transplant recipients. First-dose effects with fever, chills, headache, hypotension and pulmonary symptoms are usually mild. Severe anaphylactoid reactions are rare. A pre-sensitization of the patient against horse/rabbit globulin can be excluded by intradermal testing before ATG-administration. Sensitization during treatment and subsequent serum-sickness can be prohibited by coadministratiion of AZA. To avoid severe lymphocytopenia and

subsequent over-immunosuppression the lymphocytic count in peripheral blood proved to be a useful guideline for dosage.
The target levels of lymphocyte-counts for treatment with ATG Merieux are:

< 150/µl no ATG
> 150/µl 1,5 mg/kg ATG infused
> 300/µl 2,5 mg/kg ATG infused

In patients treated for refractory SV no severe, life-threatening side-effects occurred. The risk of CMV-infection or -activation is less than in transplant-recipients. The risk for CMV-infection increases inversely with lymphocyte-count. Mild thrombocytopenia as well as leucopenia may also occur.
Production of ATG and mode of action: IgG-fractions of ATG are produced in rabbits or horses. The sources of antigens differ: thymic or thoracic duct cells or continuous T-cell lines (e.g. Jurkatt cells) are used as immunogens. In vivo ATG leads to absolute lymphocytopenia, mediated by cell opsonization and subsequent destruction. T-cells that reappear after cessation of treatment are functionally impaired and immunosuppression lasts on.
Thymoglobulin Mérieux is produced by selection of the IgG-fraction with the highest concentration of lymphocytotoxic antibodies after immunisation of rabbits with human thymocytes. The end-product is highly purified and lyophylized. The efficacy has been proven in vitro by a lymphocytotoxicity assay with human lymphocytes.
Administration of ATG: ATG should be diluted in 250-500 ml of physiological NaCl solution and infused over 4 h via a central venous line or a large-caliber peripheral vein. To prevent allergic reactions the patient should be tested for hypersensitivity with an intracutaneous test of ATG testserum.

5. Hypothesis of **SOLUTION**
ATG is able to induce remission of SV refractory to standard treatment and is useful to achieve long intervals of remission in frequent relapsers in whom standard treatment should be avoided.

6. Study design
The study is planned as on open, prospective trial to study the efficacy of ATG-treatment in 20 patients with refractory SV. Patients will be followed for 15 months. The study will be performed after informed consent of the participants. The approval of the local ethical committee is needed.

6.1 Patients

Two groups of patients will be included:

a. Patients with progressive, unresponsive SV despite standard-treatment with cytotoxic agents and OCS and/or other unsuccessfully administered immunosuppressive drugs. Severe organ-damage attributable to SV is imminent in these patients and effective medication to induce remission is desperately needed. ATG is given with the intention to induce remission or at least to improve the patient´s condition.
The induction of remission in these patients is the primary end-point, maintenance of remission and sparing of other immunosuppressants are secondary end-points.

b. The second group of patients are those who have constant grumbling disease and who tend to relapse after reduction or omission of cytotoxic agents. These patients may not necessarily have severe, life-threatening disease at the time of inclusion. Still, the „dependency“ of clinical-remission on cytotoxics with the associated risk of severe side-effects in these patients justifies the effort to induce longer-lasting remissions with ATG-treatment. In this group patients will be included in whom further treatment with CYC has to be avoided because of already apparent CYC-intolerance.
Maintenance of clinical remission after ATG and dose-reduction of other immunosuppressants are the end-points.

Inclusion criteria:

1. The patient has histology-proven or serology-proven WG or MP (no recent biopsy needed).
2. The patient has frequently relapsing disease and standard treatment with CYC has to be avoided **or** the patient has progressive, life-threatening disease despite standard treatment.

   Standard treatment should be avoided in the following situations:

   - CYC: bone-marrow failure with persistent thrombocytopenia (platelets < 100.000/μl), leukopenia (WBC < 3.000/μl), myelodysplasia, bladder disorders (hemorrhagic cystitis), pulmonary fibrosis, toxic hepatitis. An excessive previous cumulative dosage or any other side effect known to be associated with CYC may also be sufficient to include the patient. Second line cytotoxic treatment (e.g. AZA or methotrexate) may have been used as an alternative for at least 6 weeks.
   - AZA: bone marrow failure as in CYC, liver function abnormalities, allergy.
   - OCS: intolerable side effects (discuss with co-ordinator).

Exclusion criteria:

1. Allergy against rabbit/horse proteins
2. Previous treatment with anti-lymphocyte antibodies
3. Patient aged under 18 or over 75 years
4. Previous malignancies
5. HIV-infection
6. Inadequate contraception in fertile women
7. Pregnancy
8. Uncontrolled infection
9. Refractory congestive heart failure or fluid overload
10. Co-existence of another multi-system autoimmune disease, e.g. SLE.
11. Thrombocytopenia <50.000/ μl

6.2 Documentation of treatment-success:

Since only a limited number of patients will be eligible for the trial, there is a demand for objective success-criteria. The effect of treatment on disease-acitivity and further organ-damage will be assessed with the VITAL-score at entry and at defined intervals. VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS), the Vasculitis Damage Index (VDI) and the Short-Form-36 (SF-36) functional assessment. At some time-points, as indicated in the time-table, only the disease-acitivity by BVAS and the quality of life by SF-36, instead of the complete VITAL-score, will be assessed.
In addition the patient should regularly consult specialists, e.g. ophthalmologists, ENT-doctors etc, to obtain independent statements on disease-progression in their specialties.
Whereever possible, histological information should be obtained on several occasions during the course of the study. Depending on the individual disease-manifestations, repeated radiological imaging may help to document the course of the disease and should be encouraged.
At entry the duration of SV should be documented, as well as the number of relapses and the longest interval of remission. All immunosuppressive medication should be documented and the cumulative dosage of cytotoxics calculated.

Entry
VITAL score
History of SV including number of relapses, cumulative immunosuppressive dosage, intervals of remission
Full blood count and white cell differential
C-reactive protein, ANCA, ANA, Cryoglobulins, complement, anti-GBM-ab, rheumatoid factor, T-cell subsets (optional)
S-creatinine, GFR
AST,ALT, AP, albumin, glucose
Hepatitis B, C-serology and HIV
Urinalysis, 24h urine protein
radiological imaging (at least chest and sinus X-ray)
histology

14 day data
Medication
Full blood count and white cell differential daily
C-reactive protein, ANCA, CMV-early antigen
T-cell subsets (optional)
S-creatinine, GFR
AST,ALT, AP, albumin, glucose
Urinalysis, 24h urine protein

1 month data
BVAS, SF-36, medication
Full blood count and white cell differential
C-reactive protein, ANCA, CMV-early antigen
S-creatinine, GFR
AST,ALT, AP, albumin, glucose
Urinalysis, 24h urine protein
radiological imaging

3 monthly data
VITAL or BVAS and SF-36 (see timetable), medication
Full blood count and white cell differential
T-cell subsets (optional)
C-reactive protein, ANCA
S-creatinine, GFR
AST,ALT, AP, albumin, glucose
Urinalysis, 24h urine protein
radiological imaging
histology

Time-Table

time (months)	**clinical review**
0	VITAL; entry data
0-0,25	ATG-treatment, documentation on separate sheet (page 11)
0,25	14 day data
1	BVAS, SF-36, 1-month data
3	BVAS, SF-36, 3-monthly data
6	VITAL, 3-monthly data
9	BVAS, SF-36, 3-monthly data
12	VITAL, 3-monthly data
15	BVAS, SF-36, 3-monthly data

6.3 Withdrawal
Withdrawal on patient´s or patient physicians request.

6.4 Adverse-effects
All drug-related adverse-effects will be recorded in the Patient Record Book.

6.5 Statistical analysis
Since no standard treatment for refractory SV is available the ATG-therapy is considered to be experimental and no formal power-calculations are possible.
For each group separately an interim analysis will be performed after the inclusion of six patients with at least one month of treatment; having two or more failures the treatment will be stopped for this group, with no or one failure the group will be extended to 12 patients.

6.6 Ethical considerations
Approvals from local ethical committees are needed. Patients will be entered after having given informed consent. Confidelity of data will be respected.

6.6.1 International Review Board
An international board will be consulted after entry of ten patients to review the incidence and severity of adverse events, the conduct of the study and communication of the study´s results.

6.6.2 Duration
Patients will be recruited for 2 years after the trial started.

6.6.3 Coordination
Rainer Nowack, Luis F. Flores Suárez and Fokko J. van der Woude
Vth Medical Clinic
Klinikum Mannheim
Faculty of Medicine of the
University of Heidelberg
Theodor-Kutzer-Ufer 1-3
D-68135 Mannheim
Tel. 0621/383 2340
Fax.0621/383 3804

6.7 Interventions

ATG will be given daily during ten subsequent days. The first dose should be 2,5 mg/kg body weight. The further dose is adjusted to the lymphocyte-count. Lymphocytes have to be counted daily. In case of severe leucopenia or thrombocytopenia no ATG will be infused.

To prevent serum-sickness, AZA will be given throughout the ATG-treatment (2 mg/kg). One hour prior to the first infusion of ATG 100 mg methylprednisolone as well as an anti-histamine has to be given. For subsequent infusions the dosage of methylprednisolone can be reduced to 50 mg.

After the course of ATG the further use of immunosuppressive drugs has to follow clinical demands and is not prescribed by the protocol. However, the drugs and their dosage have to be carefully documented for evaluation.

Day	Date	Dose of ATG	WBC	lymph	platelet	adverse effects
	d/m/y	Mg	$x10^9$/L	$x10^9$/L	$x10^9$/L	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

6.8 Concomitant therapy:

Cytotoxic agents, i.v. immunoglobulins or plasma exchange should be discontinued before ATG-treatment. Corticosteroids should be reduced to no more than 25 mg/day and cotrimoxazole should be lowered to pneumocystis carinii prophylactic dosage (1 tablet 480 mg/d).

7. References

1. Fauci AS, Haynes BF, Katz P, Wolff SM: Wegener`s granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983, 98: 76-85.

2. Borleffs JCC, Derksen RHWM, Hene RJ: Treatment of Wegener`s granulomatosis with cyclosporin. Ann rheum Dis 1987; 46: 175.

3. Jayne DRW, Esnault VLM, Lockwood CM: ANCA idiotype antibodies and the treatment of systemic vasculitis with intravenous immunglobulin. J Autoimmun 1993; 6: 207-219.

4. Lockwood CM, Thiru S, Isaacs JD, Hale G, Waldmann H: Long-
term remission of intractable systemic vasculitis with monoclonal antibody therapy. Lancet 1993; 341: 1620-1622.

5. Hagen EC, de Keizer RJW, Andrassy K, van Boven WPL, Bruijn JA, Van Es LA, et al: Compassionate treatment of Wegener`s granulomatosis with rabbit anti-thymocyte globulin. Clin Nephrol 1994; 43: 351-359.

6. Tarkowski A, Lindgren I: Beneficial effects of Antithymocyte Globulin in severe cases of progressive systemic sclerosis. Transplant Proceed 1994; 26(6): 3197-3199.

7. Tarkowski A, Andersson-Gare B, Aurell M: Use of Anti-thymocyte globulin in the management of refractory systemic autoimmune diseases. Scand J Rheumatol 1993; 22: 261-6.

8. Appendix:

8.1 Disease definitions:

Wegener´s granulomatosis
Generalized WG is characterized by granulomatous inflammation of the respiratory tract, together with necrotizing vasculitis affecting small to medium-sized vessels; necrotizing glomerulonephritis is common and reflects renal involvement. A c-ANCA pattern by IIF, with anti-Pr3 reactivity by ELISA, is found in the majority of untreated patients with generalized WG; some studies have found a minority of cases to have anti-MPO instead of anti-Pr3. In WG with disease limited to the respiratory tract, ANCA positivity is less frequent.

Microscopic polyangiitis
MP is characterized by a vasculitis predominantly affecting small vessels. Renal involvement is usual and reflected by a necrotizing glomerulonephritis. Granulomata are absent. Arteritis of small or medium-sized arteries may also occur. MP is associated with ANCA specific for MPO or Pr3, a minority of MP patients are ANCA negative or recognize other ANCA-antigens.

Renal-limited vasculitis or Idiopathic rapidly progressive glomerulonephritis
Isolated pauci-immune necrotizing and crescentic glomerulonephritis, typically known as idiopathic rapidly progressive glomerulonephritis (idiopathic RPGN) has many features to suggest that it represents a renal-limited form of MP or WG, including the presence of circulating anti-MPO or anti-Pr3 antibodies.

8.2 ATG dose regimen

ATG should be given daily during ten subsequent days. The first dose should be 2,5 mg/kg body weight. Every day lymphocytes must be counted.

The target levels of lymphocyte counting are 50-150/μl -
< 150/μl no ATG
> 150/μl 1,5 mg/kg ATG infused
> 300/μl 2,5 mg/kg ATG infused

Rabbit-anti-human ATG (Mérieux, France) will first be dissolved in the implemented solvent and thereafter in 500 ml saline or isotonic dextrose. The solution will be infused via central venous line or a large caliber vein over 4 h. Intracutaneous or conjunctivial testing of ATG to exclude a presensitization will have to be performed prior to infusion following the instructions of the manufacturer.
To prevent serum-sickness, AZA will be given throughout the ATG-treatment (2 mg/kg). In case of severe bone-marrow failure, administration of AZA should be discussed with the coordinators. One hour prior to the first infusion of ATG 100 mg methylprednisolone as well as an anti-histaminic agent has to be given. For subsequent infusions the dosage of methylprednisolone can be reduced to 50 mg and the anti-histaminic drug can be administerd orally.

8.3 Monitoring and interventions during ATG-infusion

Blood pressure and temperature should be recorded ½ hourly for the first hour and hourly for the remained of the infusion.

If pyrexia, and/or rigors occur, the infusion rate is decreased and i.v. corticosteroids (e.g. hydrocortisone 100 mg) are administered. When chills have passed (usually within 1-2 hours) the infusion will be continued.

8.4 Prophylaxis

1. Cotrimoxazol 1 tablet (480 mg) daily as Pneumocystis carinii prophylaxis.

2. Amphotericin-B suspension or tablets as Candida albicans prophylaxis.

3 Ranitidine as H2 blocker.

Clinical trial: Patient Information sheet.

Treatment of refractory Systemic Vasculitis with Anti-thymocyte Globulin (ATG)

You suffer a form of inflammation of your blood vessels, also known as vasculitis. This can affect your upper respiratory tract (nose, throat, ears), eyes, kidneys, lungs, joints, heart, nerves. In severe cases, and if left untreated, it can lead to loss of function of those organs and even to life-threatening conditions. The standard treatment for this condition consists of combining steroids and cyclophosphamide tablets which can control the disease in most patients.

The side effects of this therapy are lowering the blood cell count, stomach irritation, sleeping disturbances, weight gain, hair loss or gain in some areas, infections, bladder irritation, thinning of bones (osteoporosis), higher cholesterol levels in blood, high blood pressure, liver inflammation, infertility, skin rashes, thinning of the skin with easy bruisiness, in some cases cataracts, and increased risk of developing cancer

Unfortunately, these side-effects limit the dosage of those drugs to avoid severe treatment complications. Some patients must never be treated with cyclophosphamide because they develop such side-effect promptly. In other patients the disease progresses despite of steroid and cyclophosphamide medication. For those patients, who either do not tolerate standard therapy or have progressive disease despite it, alternative therapy is needed.

During the last years, some studies have shown that anti-thymocyte globulin (ATG) can be helpful for severe autoimmune diseases, like vasculitis. We want to document in this study whether using ATG in patients with vasculitis can be used to induce remission of refractory cases, and if it can be used in those patients who have relapsed and cannot tolerate the standard treatment.

ATG consist of antibodies against a special population of human white cells, called lymphocytes which play a role in the development of the vascular inflammation. These antibodies are produced by injecting those cells to rabbits, and recovering the antibodies they have formed, which after injection, will decrease the number and function of the lymphocytes.

ATG will be administered intravenously through a central venous catheter, which is placed on your neck under local anaesthesia. The compound will be diluted and infused over a period of 4 hours. The whole treatment lasts for 10 days, so in total a maximum of 10 applications are needed. During the period of treatment, we will ask you to take another drug, azathioprine, to prevent allergy to the compound (ATG), and blood samples, urine analysis and radiographs will be taken periodically during the study, which is intended to last 15 months.

As with other drugs, some side effects may occur. In the case of ATG, as it is derived from rabbits, a type of allergy to the proteins of these animals can occur. It is usually mild and consists of headache, fever, skin rash, joint pain and occasionally inflammation, chills, malaise, low-blood pressure, localized swelling, and in some instances, pulmonary symptoms which can include respiratory difficulty. A doctor or a nurse will be present during the treatment in case you experience discomfort. To avoid some of these symptoms, prior to applying the ATG, a test will be performed to see if you are prone to develop those reactions by injecting under your skin a small amount of the compound; however, lack of symptoms during this test does not guarantee they won´t be present during the infusion, although this is not expected to occur. Also, if you are suitable for the treatment, steroids and anti-histaminics will be given before ATG to diminish the chance of those effects to be present.

Other adverse but less common reactions are proneness to infections, which is related to the amount of white blood cells, to developing cancer, though there is not definitive proof of that. All these effects are related to the dose used and the duration of treatment.

Any other medication you have been previously taking or receiving (cyclophosphamide, intravenous immunoglobulin, plasma exchange) should be stopped before treatment with ATG. Steroids will be reduced to no more than 25 mg/day, so you will be still taking them if you already do, and 2 antibiotics, co-trimoxazole and amphotericin B will be given during the whole treatment period to prevent infections. If you are allergic to those drugs we ask you to inform us, because you won´t be able to receive them then.

If you are allergic to rabbit or horse compunds, have received treatment with similar substances before, have had cancer, are pregnant or host the AIDS virus, we ask you please to inform us, as treatment with ATG can be dangerous to you.

Your personal medical information may be scrutinised by properly authorised persons, but will be kept strictly confidential. Details of your case will be stored anonymously on a computer, but will not be available to anyone not directly involved in this study, and the computer will not be connected toany computer networks.
You are a patient with vasculitis and the standard therapy could apparently not stabilize your condition or has to be avoided. Treatment with ATG is a promising therapeutic option in this situation. We ask you to participate in the study and to agree that the treatment effect can be documented in a standardized way.
If you do not wish to take part in this study, your treatment will not be affected in any way; you can also withdraw from the study at any stage without giving an explanation and without influencing the care your receive from your health care team.
If you have further questions please contact:

Dr. Tel.

I have been informed about the nature of the therapy protocol of vasculitis with ATG. It has been explained to me, and I am willing to take part on it. Also, I have been told I can quit from participating on it, anytime I desire.

Name of the patient

Date and signature of the patient

Name and signature of the physician