Model Intervention Informed Consent

Type 1 Diabetes TrialNet Protocol TN-19

Effects of Low Dose ATG (Thymoglobulin®) Used Alone or in Combination with GCSF (Neulasta®) on the Progression of Type 1 Diabetes in New Onset Subjects

Project Description

You (you means you or your child) are being asked to take part in this research study because you have developed type 1 diabetes within the last 3 months. Type 1 diabetes is an autoimmune disease. This means that the immune system, the part of the body which helps fight infections, mistakenly attacks cells that produce insulin in your body. The cells that produce insulin are called beta cells and are found in your pancreas. As the immune system destroys these cells, the ability to produce insulin decreases and diabetes develops.

The investigators carrying out this study are part of a group called TrialNet, which is studying type 1 diabetes (T1D). These investigators are testing a medication, called ATG (Thymoglobulin) given alone and in combination with GCSF (Neulasta) as a possible treatment for people with newly diagnosed type 1 diabetes.

ATG is given by infusion (through a vein) and is approved by the U.S. Food and Drug Administration as a treatment to protect organ rejection after transplantation. GCSF is given by injection and is approved for use in people undergoing chemotherapy for cancer. GCSF has also been tested in the treatment of autoimmune diseases. We have recently completed a small study giving individuals with T1D low dose ATG in combination with GCSF. Results from this study suggest that combination treatment may preserve insulin secretion after diagnosis.

Based on these findings, the goal of this study is to conduct a larger, more conclusive study, to learn if low dose Thymoglobulin (ATG) used alone or in combination with Neulasta (ATG/ GCSF) could help people with newly diagnosed type 1 diabetes by delaying or stopping the further destruction of beta cells.

This consent form tells you about the study and what people in the study will be asked to do. The study will be explained to you and you will be given the chance to ask questions. You will be given a research volunteer handbook that explains the overall study. Taking part in this study is your decision.

If you agree to take part in the study, you will be asked to sign this consent form. You will be given a copy of the consent form to keep for your records.

Procedures

There are two parts to this study, a treatment phase that lasts three months and a monitoring phase that lasts 21 months.

Treatment Phase
The treatment phase is completed in the first three months. The first part of the treatment phase (inpatient visit) involves you staying overnight for 2-3 days in a hospital or research setting. The second part of the treatment phase requires 5 outpatient visits every two weeks.

At the in-patient visit, you will be randomly placed into one of three treatment groups. One group will receive ATG infusions given through a vein and GCSF injections. Another group will receive ATG infusions and placebo injections. The third group will receive placebo in both the infusion and injections. A placebo looks like medicine, but has no medicine in it so that people in the study will not know whether they are receiving the drug or placebo. You will be placed into one of these groups by chance (similar to drawing straws). You will have a 1 out of 3 chance of getting ATG alone, ATG and GCSF, or placebo. Neither you nor your doctor will be able to choose the group in which you will be placed. Neither you nor your doctor will know who is getting ATG or ATG and GCSF and who is getting placebo.

You will receive two treatment infusions of ATG or placebo given at the research site over a period of 2-3 days and one treatment injection of GCSF or placebo after completing the second infusion. If you are assigned to receive ATG, you will receive a total of 2.5 mg/each kg of body weight.

The study treatment infusion of ATG or placebo is given by placing a needle and/or plastic tube (IV) in your arm. This IV will be left in place for the duration of the visit which will take 2-3 days. You will be given two infusions of ATG or placebo. The first study treatment infusion will be given continuously and will take between 12 to 20 hours. There will be 12-24 hour break between infusions. The second infusion will take from 8 to 16 hours. The length of the visit and the time for each infusion depends on whether you are have reactions or side effects from the study treatment.

At least 30 minutes before each infusion you will receive acetaminophen, an antihistamine to prevent or decrease the immediate reactions to the study treatment as well as another medication called methylprednisolone or placebo which is used to suppress inflammation. Additional acetaminophen or antihistamine will be given as need to treat any reactions to the study medication. You will also receive methylprednisolone or placebo 12 hours after the start of each infusion.

During the study treatment infusions you will be checked frequently for any side effects.

Beginning at the time the infusion starts we will check how you are feeling and measure your temperature, blood pressure and pulse every 30 minutes for the first two hours and then every hour until the infusion is completed.

Study Treatment Injection Procedure:
Approximately 6 hours after you have completed the study treatment infusion you will get the first of 6 study treatment injections. The injection is given subcutaneously (a shot under your skin) just like insulin. After you go home, you will return to the study site for 5 additional injections to be given every two weeks, over the following ten weeks.

After the treatment phase is done, you will be monitored closely. We will remain in daily contact with you the first two weeks of the study.

Monitoring Phase
After completing the treatment phase, you will be monitored regularly. You will come to the study site every three months for 2-hour Mixed Meal Tolerance Tests (MMTT) at the 3, 6, and 9 month visits. You will have a 4-hour MMTT at the 12, 18 and 24 month visits. During the second year of the study will come in every six months for MMTT visits and other blood tests.

Other study procedures:
During study visits we will ask questions about your health, diet and activity, and experience as a research participant. We will periodically perform a physical examination and take blood for testing. Females will also give regular urine samples to be checked for pregnancy.

The blood tests will help us monitor your diabetes, your immune system, and your general health.
The total amount of blood drawn for tests done at each visit will not exceed the amount that is safe for your age and weight and will not exceed 8 tablespoons. More information about the specific blood tests can be found in the research volunteer handbook.

- **Mixed Meal Tolerance Test (MMTT)**

The study requires that you have **7** MMTTs to find out how much insulin your pancreas is still making. The MMTT will be done every three months during the first year and every six months during the remainder of the study.

Before each MMTT, you will get special instructions about diet and insulin dosing. To make the blood sampling easier for the test, an intravenous needle and plastic tube (IV) will be placed in your vein. The IV will be kept in place during the test. Two blood samples taken ten minutes apart (one teaspoon of blood for each sample) will be taken through the IV. You will then be given a drink called Boost, the “mixed meal”. This drink will raise your blood sugar and cause your body to produce insulin. After drinking Boost, one-half teaspoon of blood will be taken through the IV at regular intervals for 2 hours. The total amount of blood taken for the MMTT will not be greater than 2 tablespoons for the two hour test and 3 tablespoons for the 4 hour test.

- **Diabetes Care**

If you decide to be in this study, you will receive what is called “intensive management” of your diabetes. The goal of this type of treatment is to keep your blood sugar as close to normal as possible. This will require you to take enough daily insulin injections to meet this goal. You could also be on an insulin pump instead of injections. During the study you will need to check your blood sugar levels frequently, and report them as often as once every two weeks to the study team. Your research study team will work with your personal diabetes health care team to keep your diabetes under good control.

Blood Samples for Understanding Type 1 Diabetes

An important part of this study is to better understand what causes type 1 diabetes, how individuals respond to treatments, and to get ideas about new treatments in the future. While TrialNet is ongoing, these samples will be used only by TrialNet approved researchers. As such, we may be collecting blood samples including genetic samples for these studies at most of your visits. You will not routinely be provided with test results from these studies.

Risks and Discomforts

The treatment and tests involved in this research project have the known risks listed below. There may be other risks that are not possible to predict.

ATG:
Common Side Effects:

Frequent side effects of ATG include: low blood counts for white blood cells (the cells that help fight infections), headache, back pain, and joint pain.

During the inpatient visit, you may experience “cytokine release syndrome (CRS)”. Symptoms of CRS include; nausea, vomiting, fever, chills, and increased heart rate. These side effects most often resemble a mild flu. To help reduce these symptoms you will be given medications before each ATG infusion (*acetaminophen, antihistamine*, *and methylprednisolone as described above).*

You may also have another type of reaction called “serum sickness”. If serum sickness occurs, it is expected 1-2 weeks after the ATG infusion. The symptoms of serum sickness may include the following: fever, itching, rashes, muscle or joint pain, swelling and a general feeling of unease. The study doctors will provide medicines to treat serum sickness if it occurs.

Uncommon Side Effects:

Rare but serious side effects include infections, allergic reactions, and bleeding.

Allergic Reactions: A reaction to ATG may occur in people who are allergic to rabbits because the drug contains rabbit proteins. This reaction could be a skin rash or trouble breathing within the first hour of the infusion. The study doctors will start the ATG treatment at a low dose, and will give it very slowly. If symptoms develop and become severe, the study doctors will slow the infusion even more or stop it for a period of time. If necessary, they can give you more of the same medications and/or other medicines to help reduce allergic like symptoms. Such side effects include: chest pain, diarrhea, shortness of breath, fever, shivering, low blood pressure, lack of appetite, dizziness, itching, sweating, and hives and could occur within the first hour of the infusion.

In very rare situations, some people have a severe allergic reaction to ATG called anaphylaxis. Anaphylaxis could be life-threatening, with symptoms that include difficulty breathing and a fall in blood pressure severe enough to cause shock. Due to the seriousness of this reaction, you may require other medicines to recover. In the unlikely event that this happens, you will not receive any more study medication.

Infections: You may be at a higher risk for getting infections for about 3 months after receiving ATG. To prevent you from getting infections, you will be followed closely by the study doctors. You should contact your study doctor if you develop any infections, or bruising or abnormal bleeding, or you are not feeling well at any time.

You should avoid direct contact with anyone who you know has an infection during this time.

Bleeding: Rarely, bleeding may occur. ATG may cause the number of platelet cells in your blood to decrease. Platelets help your blood clot. If they decrease to very low levels there is a higher risk for bleeding. Your platelet count will be monitored each day before ATG is given. If the level falls into a range that is considered high risk for bleeding, then the drug dose will either be reduced or held. If the platelet count recovers to an acceptable range in one to two days, then the ATG will be given again.

GCSF:

There are also some risks associated with receiving GCSF. While taking GCSF your white blood cell count may become elevated. This could cause your spleen to become enlarged. In some instances an enlarged spleen could increase your risk for splenic rupture which could be life threatening. Call your study doctor immediately if you have pain in your upper left abdomen or left shoulder. GCSF therapy has also been associated with breathing problems in a small number of patients who received the drug as part of cancer therapy. GCSF also carries a 10-20% risk of bone pain and a less than 10% risk of fever, pain or redness at the site of injection, headache, and dizziness.

Unknown Risks: The experimental study treatment may have side effects that no one knows about at this time. Medications like ATG and GCSF that alter responses by the immune system can possibly lead to an increased risk of certain types of cancer. The risk of cancer is unknown but is thought to be very small. An increase in the rate of cancer has not been seen in previous studies of people given either medication.

- **Birth control and pregnancy**

It is not known whether ATG or GCSF can damage unborn babies. If you could become pregnant, you will need to use an effective form of birth control during the first 3 months of participation in the study. This is for safety during the treatment part of the study. Women must not become pregnant for two years from starting the study. If you become pregnant, you must tell the study doctor right away. We will stop your study medicine.

- **Intravenous Needle (IV) and Blood Drawing**

While on the study you may have side effects from having your blood taken or IV placed. The risks of side effects from these procedures are very small. There is sometimes soreness and/or a bruise at the site where the needle goes through the skin. Once in a while, people faint. It is rare, but some people may get an infection, a small blood clot, swelling of the vein and the area around it or bleeding where the needle goes through the skin.

- **Genetic Testing**

We will try to understand how genes and gene function may relate to diabetes and ATG given alone or in combination with GCSF. We will not provide the results of your genetic testing to you or anyone else. Although we will try very hard to keep any information about your genetic testing private, there is a very small possibility that someone else could learn about your testing.

- **Vaccines:**

Some types of vaccinations ("live" vaccinations) may not be safe during the treatment period. If you need any "live" vaccinations, you should get them more than six weeks before enrolling in the study. Other types of vaccines (other than live vaccines) might be less effective in people whose immune systems are less active. We don't know if ATG will have this effect. Nonetheless, we do recommend that you get an influenza vaccine during flu season. Be sure to talk to your study team before getting influenza vaccine during flu season as the timing of this is important and will depend on when you completed the ATG infusion.

Except for the "flu shot" you should not have any other vaccines during or for three months following the treatment phase of the study. After that time, be sure you let us know if you have received any vaccines as part of your usual medical care.

- **Mixed Meal Tolerance Test (MMTT):**

The MMTT requires that you drink a product called BOOST which contains milk and soy ingredients. People with severe allergies to these could have a reaction. If you have a known allergy to either of these ingredients, please let us know. It is possible we may need to advise you not to participate in the trial.

Benefits

If you decide to take part in this study, there is no guarantee that your health will improve. It is hoped that the ATG given alone or in combination with GCSF will help your body continue to make insulin, but there is no guarantee that this will happen. Even if the study drug can protect the insulin producing cells that are left, you will still need to take insulin shots. Studies have shown that people who continue to make insulin have less trouble with low blood sugars and fewer complications from their diabetes than people who no longer make their own insulin. We will follow your health and diabetes closely.

Study Duration and Number of Participants

There will be at least 84 participants enrolled in the study. You will be a participant in this study for two years. After completing the study, we will invite you to be followed in the TrialNet Long-Term Investigative Follow-Up Study (LIFT) so we can continue to provide you with further information about your diabetes and learn how long the effect of treatment will last as well as any possible long-term side-effects.

Alternatives to Participation

Before you decide to take part in this study, we will talk with you about the other options available to you. You may choose not to participate in this study. There may be other research studies that you can choose to be in.

Source of Funding

The National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) is providing major funding for this study. The study is also sponsored by National Institute for Allergy and Infectious Diseases (NIAID), the National Institute for Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation (JDRF), the American Diabetes Association (ADA), and the Helmsley Charitable Trust. Sanofi will provide the ATG (Thymoglobulin) and Amgen will provide the GCSF (Neulasta) as well as the placebo injections for the study. Sanofi will also be providing additional support for the study. Roche Diagnostics will be donating blood glucose meters and strips.

Cost to Subject

There is no cost to you for being in this study. There will be no charge for procedures or drugs required by the study. You will have to pay the costs for most of your usual diabetes care supplies (insulin, needles, etc.).

Subject Payment

If you decide to be in this study you will receive a small compensation for each study visit you attend. In addition to this, we will pay for your minor travel or parking costs. By signing this consent form, you understand and agree that, if this research project results in the development of any product that can be sold, you will not receive a share of any money that

is made.

Study Withdrawal

Your choice to be in this study is completely voluntary. You may choose not to be in this study or to stop being in this study at any time, and your doctor will still take care of you. Your current or future medical care will not be changed if you decide not to be in this study or to stop being in this study at any time. Your study doctor may also choose to discontinue your study treatment at any time if it is felt that continuing treatment may hurt you. This may happen if the side effects are too great, or if you do not follow the study instructions. You will be told of any new findings that affect your being in this study.

Invitation for Questions

You will receive a copy of this consent form. Please ask questions about this study or consent at any time. You are welcome to talk about this study or consent with your family, doctor, or anyone else. The staff of the research study will be happy to discuss any questions with you. You may ask your questions to _____ at phone _____.

Confidentiality:

Your consent to be in this study gives the TrialNet researchers permission to collect personal information about you and to use it for research purposes. Personal information is information such as your name that directly identifies you. This information may be shared with other TrialNet centers as needed to help with the study. Your consent also includes permission for the sponsor of this study (NIDDK) and the Food and Drug Administration (FDA) to review your records.

If you participate in this study, you will be given a unique study code number. It will identify the information and samples collected from you from study examinations and procedures. It will be sent to the central TrialNet Coordinating Center under the supervision of the NIDDK.

A Certificate of Confidentiality has been obtained from the National Institutes of Health (NIH). This is intended to further protect the confidentiality of information that we obtain about you. By having a Certificate of Confidentiality, TrialNet researchers are not required to give information that can be used to identify you. For example, we cannot be forced to give information about you to insurance companies. Also, we cannot be forced to give information about you for any civil, criminal, administrative, or legislative proceedings whether at the federal, state or local level. However, the Certificate of Confidentiality does not prevent you from giving this information to others. Please understand that we will maintain the confidentiality of your research record. We cannot guarantee the confidentiality of test results provided to you if you wish to share them.

There are some rare exceptions to the protection offered by the Certificate of Confidentiality. TrialNet researchers are not prevented from telling about matters such as child abuse, certain infectious diseases, or threatened violence to yourself or others.

TrialNet researchers will consider your records private. Rarely, representatives of the United States Department of Health and Human Services (DHHS) or TrialNet may review or ask for a copy of your study records. If this happens, we will provide your records. Also, for auditing purposes, employees of the *(institution's name)* _____ or its agents could be allowed to see your study records to make sure that the study is being done properly.

The results of this study may be published for scientific purposes. By signing this form, you are agreeing to this. Your records and results will not be identified as belonging to you in any publication.

Payment for Injury or Harm

Taking part in this research study may hurt you (this was explained in the section called "Risks and Discomforts"). If you need to get medical care right away, you should go to the nearest emergency care center. Be sure to explain that you are participating in a research study. If you do not need emergency care, the investigator will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. You will be responsible for any costs not covered by your health insurance. TrialNet and the clinical site you go to will not pay for your care. Likewise, TrialNet and your clinical site will not pay you for pain, worry, lost income, or non-medical costs that might occur from being in this research study.

Additional Information:

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

CONSENT FORM FOR SUBJECTS (18 years of age or older) OR PARENT/GUARDIAN (if subject is less than 18 years of age)

Storage of Samples in NIDDK Repository

When TrialNet is over, we intend to put any remaining samples including genetic samples into the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) repository for future studies related to type 1diabetes and its complications. They will be stored there indefinitely without your name or any other identifying information on them, as such, once in the repository you will not be able to have them removed. Researchers must first get permission from the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) to use samples from the repository.

The following checkbox gives you the choice of allowing us to put any remaining blood samples in the NIDDK repository. Even if you decide not to have your remaining blood

samples stored, you can still participate in this study.

Are you willing to allow us to put any remaining blood samples including genetic samples in the NIDDK repository (please initial yes or no)?

_____YES _____NO

Authorization

By signing this consent form, you agree that you have read this informed consent form and that the study has been explained to you. You also agree that your questions have been answered and that you agree to be in this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a copy of this consent form.

I have read this paper about the study or it was read to me. I know what will happen, both the possible benefits and the possible risks. I choose to be (or to have my child) in this study. I know I can stop being in the study at any time, and I will still get the usual medical care. I will get a copy of this consent form.

Participant
Print Name of participant: _____

Signature of participant (age 12 or older): _____

Date of participant's signature: _____

Parent or guardian (if subject < age 18)
Print Name of parent or guardian: _____

Signature of parent or guardian: _____

Date of parent's or guardian's signature: _____

Consent obtained by:
Print name of researcher: _____

Signature of researcher: _____

Date of researcher's signature:_____