A Double-blind, Placebo-controlled, Crossover Study of Magnesium Supplementation in Patients with XMEN Syndrome

Identifier:	NCT02496676
NIAID Protocol Number:	15-I-0161
Sponsored by:	NIAID
Date:	March 26, 2018
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Continuing Review Approved by the IRB on 05/22/17
Amendment Approved by the IRB on 03/26/18 (G) Date Posted to Web: 04/06/18
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional. In this document, "you" refers to you or your child.

PURPOSE OF THIS STUDY

You have been asked to join this study because you (or your child) have a genetic condition called "XMEN syndrome" in which your cells have less magnesium than normal. This makes it difficult for the body to fight infections, especially Epstein-Barr virus. Epstein-Barr virus is a very common infection and does not cause serious illness in most people. However, because of your condition, you are at risk of developing Epstein-Barr virus lymphoproliferative disease, where the body makes too many white blood cells. In some cases, this can cause lymphoma, a type of cancer that affects the lymph nodes, kidneys, or other organs. Some people with XMEN syndrome do not develop a severe Epstein-Barr virus

infection, but do have an increased risk of other types of infections (such as herpes virus infections) and cancers (such as sarcoma).

We invite you to participate in a research study to see if magnesium supplements can strengthen your immune system (the system in your body that fights infection). To test this, we will give you magnesium supplementation and do blood tests to see if it reduces the amount of Epstein-Barr virus in your body (if you have high levels of Epstein-Barr virus in your blood to start with) or causes cell changes that are related to better immune function (if you have low or no Epstein-Barr virus in your blood to start with). Magnesium is a mineral naturally found in the body, in foods, and in all living things. We have already given magnesium supplements to a few patients with XMEN syndrome and it seemed to reduce the amounts of Epstein-Barr virus in the blood as well as the frequency of other types of infections. We also saw improved function in some types of immune cells. But we need to study more patients before we know if magnesium really works.

About 20 patients will be in the study. There are 2 parts to the study: The first part of the study lasts a total of 6 months. You will take magnesium pills for 3 months and pills that contain no nutrients at all (called "placebo") for the other 3 months. We use a placebo to see if magnesium is more or less safe or effective than not taking anything. The placebo and magnesium pills look exactly alike. Neither you nor the study team will know which one you are taking. At the end of 6 months, the study team will ask the pharmacy to reveal which type of pills you were taking during each 3-month period. From the results of your laboratory tests, the study team will learn if the magnesium pills had the effects we are looking for (reduced Epstein-Barr virus levels or immune cell changes). If they did, then you will be finished with the study. But if the magnesium pills did not have these effects, then we will ask you to participate in the second part of the study. In the second part, you will be admitted to the hospital for between 4 and 5 days to receive a liquid form of magnesium for 3 days through a vein in the arm. This is called an "infusion". Then you will take magnesium pills for 6 months. During each part of the study, the number of pills you take will increase depending on how well you tolerate them.

Patients are being asked to participate for 1 year and to visit the NIH Clinical Center about 13 times. However, if you only need to do the first part of the study, you will be finished in 6 months and there will be fewer visits. If you participate in this study, you will not be able to take any magnesium supplements or vitamins that contain magnesium during the duration of the study, except for the supplements that are provided by the study staff.

STUDY SCHEDULE

Screening visit: If you agree to participate in this study, the first visit will include the following:

- Medical history and physical exam
- Computed tomography or "CT" scan of neck, chest, abdomen, and pelvis (if not done in the last 6 months)
- Electrocardiogram or "EKG" test of the heart's electrical activity
- Blood draw for routine laboratory tests such as blood cell counts, viral load measurements of Epstein-Barr virus and cytomegalovirus ("CMV"), HIV test if not done in the past year, and research tests

HIV is the virus that causes AIDS. If you are infected with HIV then you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

You will be asked to stop taking all magnesium supplements and multivitamins that contain magnesium (if you are taking them) at least two weeks before beginning the baseline studies. During the study, we ask that you take only the supplements that are provided by the study staff.

Baseline visits:
After your eligibility has been confirmed and you have not taken magnesium supplements for at least two weeks the following blood and urine tests will be done:

- 24-hour urine collection for magnesium
- Blood draw for routine tests such as blood cell counts and blood clotting tests
- Blood tests for Epstein-Barr and CMV levels, magnesium levels and immune system measures. We will need to measure Epstein-Barr virus or other immune system markers in your blood every day for 3 days in a row, so you will need to come in to the NIH every day for these 3 blood draws.

At the end of the baseline visit, you will be randomly assigned (like the flip of a coin) to take either magnesium pills or placebo pills. You will be provided with your assigned pills and instructions for taking them.

Follow-up visits:
While you are taking the pills, you will need to come to the Clinical Center every 4 weeks for 6 months. During these visits, we will ask you how you are feeling and if you have had any problems taking the pills. We will do a physical exam, draw blood, and collect urine to repeat the tests that measure the amounts of magnesium and Epstein-Barr virus in your body. We will also give you a new supply of pills at these visits. In addition to these visits, we will contact you by phone to find out how you are tolerating the pills.

3-month and 6-month visits:
At these visits, you will return to the Clinical Center for a physical exam, review of medical history and medications, blood and urine tests including a 24-hour urine collection, and EKG.

At the 3-month visit, we will give you different pills to take. If you were taking magnesium pills for the first 3 months, then you will be given placebo. If you were taking placebo, then you will be given magnesium. You will not know which one you are taking.

After you have been taking pills for a total of 6 months, if the test results show that magnesium had the effects we were looking for, then you will be finished with the study. You may choose to continue taking magnesium supplements under the care of your regular doctor.

If the tests do not show the effect that we were looking for during the first 6 months of the study, then you will be asked to participate for another 6 months. Here's what will happen if you participate in the second part of the study:

2-week washout: You will stop taking the study pills. For 2 weeks, you will be asked not take any magnesium supplements or multivitamins containing magnesium.

Magnesium infusion plus oral magnesium: After the 2-week washout, you will be hospitalized at the Clinical Center for between 4 and 5 days. During this time, you will have a physical exam, an EKG, blood tests, and urine magnesium tests. While in the hospital, you will receive infusions of magnesium solution over 3 days through a vein in your arm. After this, you will have more blood tests and be sent home with magnesium pills to take daily for about 6 months. You will return to the Clinical Center for tests 12, and 24 weeks after you start taking the pills. At these visits, we will do a physical exam, review of medical history and medications, and collect some blood and urine for testing, and do an EKG. You will do a 24-hour urine collection for the last 2 visits. After the last visit, you will be done with the study. You may choose to continue taking magnesium supplements under the care of your regular doctor.

STUDY PROCEDURES AND THEIR POTENTIAL RISKS/DISCOMFORTS

Magnesium and placebo pills: We will provide pills and instructions for taking them. In the beginning, you will start with 2 or 4 pills per day, and then increase the number of pills every 2 weeks until you are taking between 5 and 8 pills per day. As you are increasing the number of pills that you are taking, we will contact you by phone to see how you are tolerating the pills. How many you take depends on your weight and how you tolerate the pills. For children and adults who are unable to swallow pills, the pills may be crushed and mixed with juice or food.

Risks: In some people, magnesium pills may cause side effects like diarrhea and nausea. An increase in certain liver function tests detected in the blood have been seen after receiving oral magnesium. Blood tests will be done to monitor this. If you experience symptoms, then we may lower the dose of magnesium or placebo until your symptoms go away.

Magnesium can interact with certain drugs, including barbiturates, narcotics, hypnotics, neuromuscular blocking agents, and cardiac glycosides. It may also reduce the effectiveness of certain antibiotics. We will ask you if you are taking any of these drugs before giving you magnesium. If you are prescribed any new medications during the study, you should tell the doctor that you are participating in a study of magnesium supplementation.

Magnesium infusion: If you participate in the second part of the study, you will stay in the hospital at NIH for 4 to 5 days for a magnesium infusion and related tests. A tube will be placed into a vein in your arm and magnesium solution will be administered through the tube ("infused") 3 times per day for 3 days.

Risks: Insertion of an intravenous tube may cause discomfort, bruising, and rarely infection where the tube is inserted. An overdose of magnesium can cause side effects including flushing (warmth/redness of the face), sweating, low blood pressure, irregular heartbeat, slowed breathing, coma, and death. An increase in certain liver function tests detected in the blood have been seen after receiving intravenous magnesium. Blood tests will be done to monitor this. These effects are not expected to occur at the dose levels we are giving, but do sometimes occur at larger doses. While you are

receiving intravenous magnesium, we will be monitoring the levels of magnesium in your blood to make sure that you don't receive too much.

Because the magnesium solution contains aluminum, long-term magnesium infusions can cause toxic levels of aluminum to build up in people with kidney problems. Therefore, if you have kidney problems you will not be allowed to participate in this study.

Placebo and washout periods: While you are taking the placebo and when you are not taking the magnesium supplement during the 2-week washout period the Epstein-Barr level in your blood may increase.

CT scan: A CT scan will be used to check for tumors. You will lie still for a few minutes under a scanner that creates x-ray images of your organs. You will not be allowed to eat anything for 4 hours before the scan. Prior to the scan, you will be asked to drink a mildly unpleasant beverage called "contrast" and you may receive an injection of dye through a needle placed in your arm vein. You will likely have a warm, flushed sensation during the injection of the dye. During the CT scan, you will be alone in the room, but the staff will always be able to see, hear, and speak with you.

Risks: A CT scan does not cause pain, but it does involve exposure to radiation. This radiation exposure is for research purposes only and is not required for your medical care. The amount of radiation you will receive from the CT scan in this study is approximately 1.3 rem. This is within the safety limit of 5.0 rem per year set by the NIH Radiation Safety for adults, but this is higher than the 0.5 rem per year dose guideline for children. The Radiation Safety Committee, a group of experts in radiation matters, has approved this protocol even with the effective dose of radiation exceeding the guide for children because of the importance of the information to be obtained. By comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as soil, drinking water and the sun. If you would like more information about radiation, please ask the study doctor for a copy of the pamphlet, "An Introduction to Radiation for NIH Research Subjects."

Radiation exposure may very slightly increase in your risk of cancer. While there is no direct evidence that the amount of exposure received from being in this study is harmful, there is indirect evidence that it may not be completely safe. Please tell the study doctor if you have had other recent x-rays or CT scans so we can make sure you will not receive too much radiation.

The contrast agent used during the CT scan has been approved by the FDA to improve CT images. We will test your kidney function before you receive any contrast agent to make sure your kidney function is within safe limits for administration of contrast. Reactions to the contrast agent are uncommon and occur in less than 1 in 1000 people. These reactions can range from mild itching and hives to serious reactions including difficulty breathing and anaphylactic shock (low blood pressure and severe problems with breathing). Anaphylactic shock can result in death. There is also a small risk of kidney damage, but this is rare and often reversible. A physician will be present to provide immediate assistance in the unlikely event that you do experience a bad reaction to the contrast agent.

Blood draw: Blood will be drawn from a vein in your arm. We will do blood tests that tell us how your immune system, liver, and kidneys are working. We will test your blood for Epstein-Barr virus and other viruses that affect your immune

system. Some blood will be stored for future research testing. The total amount of blood collected during this study will not exceed the guidelines for blood drawn for research purposes at the NIH Clinical Center. While in the study, please tell the study staff if you are participating in other studies or will have blood drawn for any other reason.

Risks: Drawing blood involves sticking a needle into a vein in the arm. This is slightly uncomfortable but not dangerous. It can leave a temporary bruise. Rarely, an infection can happen. You may feel lightheaded or dizzy during or immediately after blood drawing.

24-hour urine magnesium test: This test will involve collecting all urine passed during a 24-hour period. We will provide a container so you can collect your urine at home and then bring it to the Clinical Center.

EKG: We will perform an electrocardiogram, a painless recording of your heart's normal electrical activity. You will be asked to lie down and small sticky pads will be stuck to your arms, legs, and across your chest. You will be asked to lie still for a few minutes, and may be asked to hold your breath for a few seconds. You will not feel anything while the ECG is performed.

Risks: There are no expected risks from this procedure. However the skin may become a little itchy and red where the sticky pads are placed.

Physical exam with medical and medication history: We will take your "vital signs" (temperature, blood pressure, heart rate and breathing rate), weight, and height. You will be asked about how you are feeling, if you've had any illness recently, and about prescription and over-the-counter medications you have taken. If you are having symptoms or complaints, then we may examine the parts of your body where the symptoms are happening.

Pill reminder card: You will be given a card to write down how many pills you took each day and if you had any problems with or symptoms from taking the pills.

POTENTIAL BENEFITS

You may not personally benefit from participating in this study. If you have an Epstein-Barr virus infection, it is possible that it may improve or resolve while you are taking magnesium. It is also possible that other infections may improve or resolve. However, we cannot be certain of this. By taking part, you may contribute new information that could benefit patients in the future.

ALTERNATIVES TO PARTICIPATION IN THIS STUDY

You can choose not to participate in this study. This decision will not affect any ongoing care or evaluations you may be receiving at the NIH. Your eligibility to participate in other research studies at the NIH will not be affected by your decision to enroll or not enroll in this study.

WITHDRAWAL FROM THE STUDY

You can stop participating in this study at any time. The decision to no longer participate in this study will in no way affect your ability to receive care at the Clinical Center or to participate in other NIH studies.

REASONS FOR ENDING YOUR PARTICIPATION EARLY

You may be removed from the study without your consent if the study doctor feels it is in your best medical interest, if you develop a condition or side effect that makes you ineligible to continue participation in this study, if the study is cancelled or stopped, or if you do not comply with the study requirements.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no charge to you or your health insurance company for any tests or procedures directly related to this study. The costs for any other medical care provided outside the NIH during this period will not be covered.

COMPENSATION

Participants will receive compensation up to $720 for the completion of Part I or $1365 for the completion of Parts I and II. Participants will be compensated at the completion of part I, part II or at the time of withdraw of the study for the portion of the study completed.

NEW FINDINGS

Any new findings that are discovered during this study, including those that may affect your willingness to continue, will be discussed with you.

STORED SAMPLES AND FUTURE RESEARCH

If you agree to participate in this study, then you also agree to let us store your blood for future research. These stored samples may help us learn more about XMEN and magnesium supplementation. The samples will be labeled with a code that only the study team can link to you. We will keep any information that can be traced back to you as private as possible. If you change your mind and decide that you do not want us to store your samples, please contact us. We will do our best to comply with your request, but cannot guarantee that we will always be able to destroy all your samples.

We may send your coded samples to other investigators for their research. We might also share information such as your sex, age, health history, or ethnicity. We will not sell your samples and you will not be paid for any products that result from the research. Future studies may require health information that we don't already have. If so, our study team will contact you. Future research that uses your samples will probably not help you, but it may help us learn more about health and disease. The research tests performed in this study are not routine medical tests and may not relate directly to your medical care. The greatest risk associated with storing samples is that someone may take information from your medical records without your permission. The chances of this happening are very low.

CONFLICT OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. You may ask your research team for additional information or for a copy of the "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH". This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Guide but are not required to report their personal financial holdings to the NIH.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines. For this protocol, the compensation plan is outlined above.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Juan Ravell, Building 10, Room 11D-13, Telephone: (301) 263-4493.

You may also call the Clinical Center Patient Representative at (301) 496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 22, 2017 THROUGH MAY 21, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____