L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital
Centre universitaire de santé McGill
McGill University Health Centre

CHU Sainte-Justine
Le centre hospitalier
universitaire mère-enfant

Université de Montréal

PEDIATRIC RESEARCH INFORMATION AND CONSENT FORM

Title : Milk Desensitization and Induction of Tolerance in Children

Name of Participant :

Persons responsible :

- Montreal Children's Hospital- McGill University Health Center: Dr Bruce Mazer

  Dr Moshe Ben-Shoshan_
- CHU Sainte-Justine : Dr Philippe Bégin

Funding Source: AllerGen NCE, Inc

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

The Allergy department participates in research studies to try to improve treatments for children with milk allergy. Today, we are inviting you to take part in a research study. Please read this information to help you decide if you want to participate in this research project. It is important that you understand this information. We encourage you to ask questions. Please take all the time you need to make your decision.

We encourage parents to include their child in the discussion and decision making to the extent that the child is able to understand.

In this research information and consent form, "you" means you or your child.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to assess a treatment protocol that may help children with milk allergy tolerate milk. This process is called Oral Immunotherapy and involves 2 treatment periods: 1) gradual supervised exposure to milk in our research unit; 2) Supervised exposure to milk at home.

BACKGROUND

You have milk allergy. Typically with patients with food allergies, treatment consists of avoiding the allergenic food and managing reactions when they occur, but not of removing the actual allergy. Recent studies have shown that people with food allergies can be made 'tolerant' (meaning they won't react to) to foods to which they had previously reacted by very slowly introducing the allergenic food. We want to see if by using our protocol, we can make patients who are allergic to milk tolerant to milk.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 84 patients will take part in this study including approximately 76 participants from this hospital.

WHAT WILL HAPPEN ON THIS RESEARCH STUDY?

If you agree to participate, you will be contacted by a member of our research team in the clinic and will be randomly assigned (like flipping a coin) to receive either oral immunotherapy (treatment group) or follow- up (control group) only during one year. During the study, participants in both groups will be invited for follow-up in which their allergy status as well as tests assessing potential tolerance to milk will be taken. We will also ask you to keep a diary documenting your symptoms during the study period. These will take no more than 20 minutes per visit to complete. In addition, a sample of 5-10 ml of blood (less than one tablespoon) will be taken from a vein in your arm initially and during the follow-up period (every 3 months for 1 year). If you agree, part of this blood will be sent to the following research laboratory in the United States to look at modifications to your IgE (the protein involved in allergic reactions) that take place during milk desensitization. These samples will not identify you in any way, and will be destroyed after five years:

The Ragon Institute of MGH, MIT and Harvard
400 Technology Square
Floor 7 Room 765
Cambridge MA 02139

Children in the follow-up only group will be invited to participate in oral immunotherapy after the follow-up year. We will also review your medical records at the Montreal Children's Hospital. This will enable us to determine the tests performed in order to diagnose your milk allergy.

You will be contacted every 1-3 months by our research team (either by email or phone according to your preference) during the following year and be asked about accidental exposure and potential allergic reactions.

Oral Immunotherapy (OIT)

Oral Immunotherapy for milk is a way to allow people with milk allergy to eat the food they're allergic to without having a reaction. There are four stages to Oral Immunotherapy (OIT).

Blinded Oral Milk Challenge

The first stage of OIT is a blinded oral milk challenge. This is done to be absolutely sure that you are allergic to milk. During the challenge, you will be given bigger and bigger amounts of milk, alternating with something that you are not allergic to, like soy or rice milk. The challenge is blinded, meaning that you will not know if you receive the milk or the soy/rice milk first.

The way the challenges work is as follows:

1. Your child will come to the hospital in the morning. He/she will have an intravenous line put in his arm. This is so that if he/she has an allergic reaction, medication to treat the reaction can be given as quickly as possible.
2. Once your child has the intravenous put in, he/she will be given a small dose (0.1 ml) of either milk or soy/rice milk. You will not be told which one he/she is getting.
3. Every 10-15 minutes, your child will be given a larger amount of milk or soy/rice milk, up to 60 ml (4 tablespoons).
4. In the afternoon, the same procedure will be followed, but this time with the other product – thus if he/she had soy/rice milk in the morning, he/she will have milk in the afternoon, and vice versa.
5. If the study doctor feels that your child had an allergic reaction to either the soy/rice milk or cow's milk, the challenge will stop, your child will be given medication to treat the allergic reaction and will not take any more of the product.
6. To ensure that your child is safe and doesn't have a late reaction, he/she will stay at the hospital under the observation of the study staff for at least two hours after the end of the challenge. If your child reacts to milk but not to the soy/rice milk, he/she will be considered to have had a positive challenge, and thus be eligible for the study.

Desensitization Phase

This phase lasts two days and is designed to make your child less sensitive to milk, meaning that he/she will be less likely to react to milk if he/she is ever exposed to it.

1. On the first day, your child will come to the hospital and, like with the oral challenge phase, have an intravenous put in his/her arm. He/she will then be given 1 ml of very diluted milk (1 part milk in 99 parts water).
    a. One hour later he/she will be given 2 ml of the diluted milk.
    b. This hourly doubling of the amount of diluted milk that your child will take will go on until he/she reaches 8 ml.

    c. If this dose is tolerated, your child will then get 1.6 ml of less diluted milk (1 part milk in 9 parts water). This dose will be the last one given on the first day.
2. On the second day, your child will start with the same 1.6 ml of the less diluted milk.
    a. One hour later, he/she will be given 3.2 ml of the less diluted milk.
    b. This hourly doubling of the amount of diluted milk will continue until your child reaches a dose of 12 ml.
    c. If this last dose of diluted milk is tolerated, he/she will receive a final dose of 2.5 ml (half a teaspoon) of undiluted milk.
3. On both days, your child will stay at the hospital under the observation of the study staff for at least two hours after you receive the final dose

Escalation Phase

1. During this phase, your child will start by taking a daily dose of 2.5 ml of milk at home. This will continue for two weeks.
2. After two weeks, your child will come to the hospital and, under the supervision of the study staff, will drink 4 ml of milk.
3. For the next week, your child will take daily doses of 4 ml of milk at home.
4. At the end of the week, he/she will come back to the hospital and again under the supervision of the study staff, drink 6 ml of milk. This dose (6 ml) will be taken daily at home for a week. This process of coming to the hospital, drinking a slightly larger amount of milk, drinking the same amount at home every day then coming back to the hospital for a bigger dose will continue for 16 weeks, by which point your child will be drinking up to 200 ml (almost a cup) a day.
5. If your child reaches a dose where he/she has a reaction, he/she will stay at the previous dose for the rest of the 16 week escalation phase.

Maintenance Phase

This phase will last twelve months.

1. For the first month of this phase your child will drink 200 ml of milk a day.
2. After a month, he/she will come to the hospital for another blinded oral milk challenge. This will be exactly the same as the one he/she did at the beginning of the study, except the maximum dose of either rice/soy milk or cow's milk will be 300 ml (a little more than one cup).
3. If your child does not react to the highest dose of milk during this challenge, he/she will be instructed to drink as much milk and dairy products as he/she likes. We recommend taking some dairy product at least twice a week, to keep up the tolerance.
4. If your child has had a reaction to a dose lower than 200 ml during the Escalation Phase, we will recommend that he/she takes the highest dose that he/she could tolerate during the Maintenance Phase. In this case, your child will not do the one-month blinded oral challenge. Rather, at the end of the 12 month Maintenance Phase, he/she will do the blinded oral challenge, to see if he/she can tolerate higher dose of milk than at the beginning of the study.

Quality of Life questionnaires

We are interested to see what effect the milk desensitization has on how you and your child view his/her milk allergy. To discover this, at four times during the study, we will ask you to fill out a quality of life questionnaire. This questionnaire has been specifically created to assess the effect having a child with food allergies has on their quality of life. The questionnaires will take about ten minutes to fill out, and will be given while you are here at the hospital for a scheduled study visit

Long-Term Follow-Up

We are interested to see how milk desensitization persists over time. To assess this, we will ask you to return to the hospital once per year for five years. These visits will be similar to those of the maintenance phase – at each of these visits, we will collect blood and saliva samples from you, we will do skin prick testing, and we will ask you to complete a Quality of Life questionnaire. These visits should take approximately thirty minutes. This Long-term Follow-Up phase is voluntary; if you do not wish to participate in this phase, you can still participate in the rest of the study. You do can always change your mind during the study if you do or do not want to participate in this follow-up phase. If you have completed the study and wish to participate in the follow-up phase, a delegated member of the study staff can come to your home at your convenience to obtain consent

FOR HOW LONG WILL YOU PARTICIPATE IN THIS STUDY?

Participation in the study will last about 16 months. This will be followed by the five year long-term follow-up

WHAT ARE THE RISKS?

If your child is assigned to the oral immunotherapy group, he/she might have allergic reactions during this treatment. These reactions can include nausea, abdominal pain, vomiting, or inflammatory disease of the esophagus (known as eosinophilic esophagitis. You may also experience skin symptoms such as hives or itchiness. Rarely, more severe reactions such as breathing problems may occur. Your child's reactions will be monitored and treated promptly during the desensitization process in our allergy unit by our team and if deemed necessary by our medical team the therapy will be stopped. You will also receive detailed instructions for treating reactions should they occur during the home phase of therapy. All subjects on treatment will be given an adrenalin auto-injector (Twinject or Epipen) as a precaution.

The risks of having blood drawn include pain where the needle is put in, minor bleeding, bruising, and fainting. A topical anesthetic (freezing) cream can be used to decrease the pain. All of these rarely occur and do not cause any long lasting problems.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Your participation in this research will provide potential benefit to your child if he/she is assigned to the oral immunotherapy treatment group and if the therapy is successful. If your child is not assigned to the receive

desensitization there will be no direct benefit. However, the information collected from this study may help us better understand and design future therapies. In addition, in case you are interested in oral immunotherapy for your child who did not receive it initially, we will offer this treatment at the end of the first year of study enrolment.

WHAT OTHER OPTIONS ARE THERE?

Instead of participating in this research project, you could choose the standard treatment, of avoiding milk and treating the reactions if you are exposed to milk. Please discuss the different options you have with your doctor.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There are no costs associated with participating in the study. We will reimburse you for travel expenses accrued through participation (eg: parking)

ARE THERE OTHER FINANCIAL ASPECTS?

No monetary compensation is offered.

HOW IS PRIVACY ENSURED?

All information obtained during this study will be kept strictly confidential. Your child's name will never appear in any publication of the results of this study. All of the information used for research will be collected under a code number and your child's name will never appear on the data collection sheets. The code list linking your child's name to the code number will be kept strictly confidential and locked in a filing cabinet. The research data will be available only to the research team and to persons taking part in managing and analyzing the research information.

The data will be kept for five years. After five years, the data we collect will be destroyed.

By signing this consent form, you give us permission to review your child's medical records at the Montreal Children's Hospital or to obtain a copy of these records if your child was seen by a physician treating your child outside of the Montreal Children's Hospital. This information is necessary to determine the status of the food allergy and the tests that were performed to confirm the diagnosis of food allergy. Your confidentiality will be protected to the extent permitted by applicable laws and regulations.

IS YOUR PARTICIPATION VOLUNTARY?

Your participation is voluntary and you should not feel any obligation. You may agree now and are free to withdraw from this study at any time. Refusal to join or withdrawal from the study will not affect your care by

your doctor. You will be informed of any new findings that may affect your willingness to continue your participation.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions about this research project or if you suffer any problems you believe are related to your participation in this research, you can call the researcher responsible for the project in your hospital:

CHU Sainte-Justine : Dr._Philippe Bégin

Montreal Children's Hospital: Dr. Bruce Mazer at (514) 412-4470

In case of emergency, please go directly to the closest emergency room.

If you would like information about your rights related to your participation in the research, you may contact the hospital Ombudsman (Patient Representative):

- Montreal Children's Hospital : 514-412-4400, ext 22223
- CHU Sainte-Justine : 514-345-4749.

RESEARCH ETHICS COMMITTEE

The research ethics committee of the McGill University Health Centre (MUHC) approved this project and will monitor the project.

CONSENT AND ASSENT FORM

Title of this research project: Milk Desensitization and Induction of Tolerance in Children

I have been explained what will happen on this study. I read the information and consent form of 8 pages including the annexes and was given a copy to keep. I was able to ask my questions and they were answered to my satisfaction. After thinking about it, I agree to, or I agree that my child will, participate in this research project.

I authorize the research team to consult my medical records or the medical records of my child to collect the information relevant to this project.

In no way does consenting to participate in this research study waive your legal rights nor release the sponsor or the institution from their legal or professional responsibilities if you are harmed in any way.

I consent to participate in the Long-Term Follow-Up phase ☐Yes ☐No Initials : _____

Name of participant (Print)	Assent of minor, capable of understanding the nature of the research (signature) or Verbal assent of minor obtained by: _____	Date

Name of parent(s) or legal guardian (Print)	Signature	Date

Name of participant (18 years +) (Print)	Signature	Date

I have explained to the participant and/or his parent/legal guardian all the relevant aspects of this study. I answered any questions they asked. I explained that participation in a research project is free and voluntary and that they are free to stop participating at any time they choose.

Name of Person obtaining consent (Print)	(signature)	Date

Addendum to consent form

Participant who has now become an adult (18)

Title of research project : Milk Desensitization and Induction of Tolerance in Children

Today, I reviewed the information and consent form that my parents signed on my behalf when I enrolled in this research project and a copy of that signed consent was given to me.

I agree to continue my participation in this research project.

I understand that my participation is free and voluntary and that I can stop participating in this research project at any time I choose.

I authorize the research team to consult my medical records to collect the information relevant to this project.

(Adapt to the context) If I withdraw, any remaining samples or data that has not already been analyzed will be destroyed.

Name of participant	Signature	Date
Name of person obtaining consent	Signature	Date