Informed Consent

Title: “Diet as adjuvant therapy in the era of biologic therapy in pediatric-onset Crohn's disease”

Introduction

Crohn's disease is one of the inflammatory bowel diseases with new cases on the rise worldwide. It is postulated to be caused by multiple causes, but in pediatrics genetics and environmental exposures including diet appear to be the main triggers.

Patients and their families often view diet as a vital component of the management and relapse prevention of inflammatory bowel disease, and studies have found that more than 50% of patients believe that food plays a role in the onset of symptoms, and nearly 70% of patients self-impose dietary restrictions, but to date, few studies have evaluated the long-term outcomes of diet in children or adults. Due to the success of diet in achieving remission in mild-to-moderate forms of the disease, and an increasing number of patients with loss of response to available medications we set out to conduct a study to evaluate the response to diet in pediatric-onset Crohn's disease patients receiving biologic therapy (infliximab or adalimumab) who have active inflammation.

To confirm these observations, studies in a sufficient number of patients are needed to objectively demonstrate this improvement.

We ask that you read this document carefully to understand what the research study is about and what your child is participating in. You may keep this document and read it at your leisure and consult it with anyone you wish before signing it before your child starts the diet. After signing, you will keep a copy of this document. By signing this document, you will be confirming that it has been explained to you and that you have agreed to participate in it. It is essential that you know the details before making a decision whether or not your child will participate.

Once you have signed the document, you may refuse to continue in the study at any time, without having to give any kind of explanation and without this reducing the quality of medical care that you should receive.

The pediatric gastroenterology section of the Hospital Italiano de Buenos Aires is interested in carrying out a study to evaluate the response to diet as a treatment in patients with pediatric Crohn's disease under treatment with biologic medication (infliximab or adalimumab) who, after induction, present at some point in their evolution calprotectin values higher than the limit value, that is, who present evidence in the laboratory of active inflammation of their intestine. So far, there are some studies done in few patients that make us suppose that the diet can help to reduce inflammation, generating remission of the disease with good tolerance.

Our institution is a regional reference center for patients with inflammatory bowel disease, including Crohn's disease, and has vast experience in treatment with biologics and diets, always supported by the pediatric nutrition service. We invite you to participate in this research study, which may allow in the future to obtain better results in these complex diseases.

Objectives of the study

To evaluate improvement of inflammation, tolerance and impact of the growth of the diet in children with Crohn's disease who are receiving treatment with biologics (Infliximab or Adalimumab) that after induction present at some point in their evolution calprotectin values higher than the normal limit value, which tells us about active inflammation.

What happens if I do not participate?

If you do not agree that your child should not participate in this study, the quality of your child's care will not be harmed or compromised.

Study Participation

Whether or not you choose to have your child participate in this study, we will provide all necessary care for the treatment of this condition.

The number of patients to be evaluated for this study to reach statistical validity is 48 patients.

At no time during the study will other modifications be made to your treatment unless your child's clinical condition requires it, according to the opinion of your child's primary care physicians.

If you decide whether your child will participate in the study, he/she will be evaluated to see if he/she meets all the conditions to enter this study. Then, it will be randomly selected who will be selected for the diet group and who will continue with their standard treatment. Patients in both groups will be set up a treatment, study and follow-up schedule with dates, as detailed below:

Phase 1: 6 weeks.Patients in the group will receive 50% of the calories calculated as diet with recommended and prohibited foods for patients with Crohn's Disease and 50% of the calories calculated as milk formula recommended for these diseases called MODULEN, produced by NESTLÉ. Your child will have his/her regular check-ups with his/her family gastroenterologist and will also have a joint interview with the nutritionist Lic. Betania Jauregui and Dr. Maria Soledad Arcucci who will guide him/her in the diet, perform a physical examination of the patient and measure growth parameters such as weight and height. In addition, questions will be asked to evaluate symptoms associated to the activity of the disease and laboratory results will be evaluated periodically requested according to the criteria of the attending gastroenterologist. Among them, at the beginning of the phase, a calprotectin should be performed, that is, a single stool sample should be submitted to the laboratory first thing in the morning. This laboratory result will tell us about the degree of intestinal inflammation at the time of collection.

Phase 2: 6 weeks. Patients in the case group will receive 75% of the calories calculated as a diet with recommended and prohibited foods for Crohn's disease and 25% of the calories calculated as a milk formula recommended for these diseases (MODULEN).

Your child will have his/her regular check-ups with his/her primary gastroenterologist and will also have a joint interview with the nutritionist Lic. Betania Jauregui and Dr. Maria Soledad Arcucci who will guide the diet, perform a physical examination of the patient and measure growth parameters such as weight and height. In addition, questions will be asked to evaluate symptoms associated with disease activity and laboratory results will be evaluated periodically according to the criteria of the attending gastroenterologist. Among them, at the end of the phase, a calprotectin should be performed as part of their usual controls.

Phase 3: Follow-up for 12 months from the beginning of the protocol. It will be evaluated by clinical history if your child during this period presented relapses or changes in the treatment.

Throughout the study, your child will be followed up by our team in the same way as usual.

Participation in the study is voluntary and free of charge. There are no financial benefits to participating in the study. This study will not result in additional expenses for you or your medical coverage.

The decision to participate or not, does not modify in any way the treatment received, nor the medical follow-up. Your primary care physician will be notified of your participation in the study.

How will I benefit from participating in this study?

You must understand that this is a research work developed and supervised by specialists of the service, who work daily in our institution and whose usual practices are reflected in this undertaking. The ultimate goal of this work is to improve medical practices, with the incorporation of new treatments based on methodologically developed clinical evidence.

Neither you nor your child will have a direct benefit from participating in this study, but the results of the study may allow future children to benefit from a more rational and specific use of treatments for Crohn's disease.

Risks of the study

The diet is not a risky treatment since it covers all the nutritional requirements of the patients. The only risk is the lack of tolerance which in fact will be one of the objectives of our work.

Confidentiality

All your data included in this study are confidential and will be treated only by the researchers, to protect your identity and privacy, according to the Law 25326 by which

you have the right to access your personal data without any cost, at least every six months, unless there is a genuine and reasonable interest. In addition, you have the right to request the rectification of your data. The National Directorate for the Protection of Personal Data, under the Agency for Access to Public Information, the controlling body of Law 25.326, is responsible for dealing with queries, complaints or claims filed in relation to any issue regarding the protection of personal data. For such purpose, it may be addressed to: Avenida Presidente General Julio Argentino Roca 710-CABA 2°floor, data personales@aaip.gob.ar, www.argentina.gob.ar/aaip. Likewise, the subject of the study has the right to have his/her personal data processed in the future if he/she decides to withdraw consent.

The handling of the information will be anonymized, so that you cannot be identified in the presentations or scientific publications of this study.

Withdrawal from the study

If the team of treating physicians or the investigators consider, according to medical criteria, that your child presents any additional risk by participating in the study, the patient will be withdrawn and the reasons for this decision will be explained to you. Thereafter, the diagnostic and treatment sequences will be as usual for any patient with inflammatory bowel disease.

Completion of the study

You may decide to withdraw your child from the study at any time by informing his/her attending physicians or by contacting them as indicated below. If you withdraw from the study, your data will not be analyzed. The decision to withdraw from the study does not change the medical follow-up or treatment in any way. The team of doctors treating you may decide at any time to withdraw your child from the study if they believe it is safer for your child's health.

In case of withdrawal from the study, the reasons will be duly explained and everything will be done to ensure that this does not affect your child's health.

Conflicts of Interest

There are no conflicts of interest of the investigators nor any relationship with the pharmaceutical industry. This is a research work developed by physicians who seek to give you a better treatment every day.

Treatment for damages or complications

In case you have any doubt regarding the diet and the study itself, please contact immediately Dr. Marina Orsi/ Maria Soledad Arcucci at cell phone (011) 1551775637 or

Licentiate in nutrition Betania Jauregui (011) 1540540272. If you suffer any damage or complication related to the procedures of this study the Hospital Italiano de Buenos Aires will take care of the medical expenses you may need.

Complications not related to this protocol will be treated according to the usual practice of our services.

Evaluation and approval of this study

This research protocol has been evaluated and approved by the Ethics Committee for Research Protocols (CEPI) of the Hospital Italiano de Buenos Aires and authorized by DHIBA during the year 2021.

Contact and Questions

If you have any questions regarding the study, you may contact Dr. Marina Orsi at 49690200 ext 9410 or Betania Jauregui (011) 1540540272. If you have any questions about your rights as a research subject, or complaints regarding this study, you should call the Research Protocols Ethics Committee, Coordinator: Dr. Augusto Perez at 011 4959-0200 ext 8425. These committees were established to help protect the rights of research subjects.

Diet as adjuvant therapeutics in the era of biologics in pediatric-onset Crohn's disease.

Consent statement

The purpose of this study, the procedures to be followed, the risks and benefits have been explained to me. I have had the opportunity to ask any questions I had, and they have been answered satisfactorily. I have been informed who to contact in case I have further questions. I have read this informed consent document and confirm that my child will participate in this study. I understand that I may withdraw my child from the study at any time without jeopardizing his/her future medical care.

Name and surname of the Patient's mother/father. Number and type of document. Signature. Date and time

Witness's first and last name. Number and type of document. Signature. Date and time

Investigator's name and surname. Number and type of document. Signature. Date and time

Informed Assent : Adolescent patients over 13 years of age

Title: “Diet as adjuvant therapy in the era of biologic therapy in pediatric-onset Crohn's disease”

Introduction

Diet as adjuvant therapy in the era of biologic therapy in pediatric-onset Crohn's disease
Crohn's disease is one of the inflammatory bowel diseases with new cases on the rise worldwide. It is postulated to be caused by multiple causes, but in pediatrics genetics and environmental exposures including diet appear to be the main triggers.
Patients and their families often view diet as a vital component of the management and relapse prevention of inflammatory bowel disease, and studies have found that more than 50% of patients believe that food plays a role in the onset of symptoms, and nearly 70% of patients self-impose dietary restrictions, but to date, few studies have evaluated the long-term outcomes of diet in children or adolescents/adults. Due to the success of diet in achieving remission in mild to moderate forms of the disease, and an increasing number of patients with loss of response to available medications we set out to conduct a study to evaluate the response to diet in pediatric-onset Crohn's disease patients (patients aged 0-18 years) receiving biologic therapy (infliximab or adalimumab) who have active inflammation.
To confirm these observations, it is necessary to perform studies in a sufficient number of patients to objectively demonstrate this improvement.
We ask you to read this document carefully to understand what the research study is about and what you are participating in. You may keep this document and read it at your leisure and consult it with anyone you wish before signing it prior to starting the diet. After signing, you will keep a copy of this document. By signing this document, you will be confirming that it has been explained to you and that you have agreed to participate in it. It is essential that you know the details before you decide whether or not to participate.
Once you have signed the document, you may refuse to continue in the study at any time, without having to give any type of explanation and without this fact reducing the quality of medical care that you should receive.

The children's gastroenterology section of the Hospital Italiano de Buenos Aires is interested in carrying out a study to evaluate the response to diet as a treatment in patients between 0-18 years old with pediatric Crohn's disease in treatment with biologic medication (infliximab or adalimumab) who after induction present at some point in their evolution calprotectin values higher than the limit value, that is to say, who present evidence in the laboratory of active inflammation of their intestine. So far, there are some studies done in a few patients that lead us to suppose that diet can help to reduce inflammation, generating remission of the disease with good tolerance.
Our institution is a regional reference center for patients with inflammatory bowel disease, including Crohn's disease, and has vast experience in treatment with biologics and diets, always supported by the pediatric nutrition service. We invite you to participate in this research study, which may allow in the future to obtain better results in these complex diseases.

Objectives of the study

To evaluate improvement of inflammation, tolerance and impact of the growth of the diet in children and adolescents with Crohn's disease who are receiving treatment with a biologic (Infliximab or Adalimumab) that after induction present at some point in their evolution calprotectin values higher than the normal limit value, which tells us about active inflammation.

What happens if I do not participate?

If you do not agree to participate in this study, the quality of your care will not be impaired or compromised.

Study Participation

Whether or not you decide to participate in this study, we will provide you with all the necessary care for the treatment of this condition.

The number of patients to be evaluated for this study to reach statistical validity is 48 patients.

At no time during the study will other modifications be made to your treatment unless your clinical condition requires it, according to the opinion of your primary care physicians.

If you decide to participate in the study, you will be evaluated to see if you meet all the conditions to enter this study. You will then be randomized as to who will be selected for the diet group and who will continue with their standard treatment. Patients in both groups will be set up a schedule of treatment, studies and follow-up with dates, as detailed below:

Phase 1: 6 weeks.Patients in the group will receive 50% of the calories calculated as diet with recommended and prohibited foods for patients with Crohn's Disease and 50% of the calories calculated as milk formula recommended for these diseases called MODULEN, produced by NESTLÉ. You will have your usual check-ups with your family gastroenterologist and you will also have a joint interview with the nutritionist Lic. Betania Jauregui and Dr. Maria Soledad Arcucci who will guide you through the diet, perform a physical examination and measure growth parameters such as weight and height. In addition, the following will be done questions to evaluate symptoms associated with the activity of the disease and laboratory results will be evaluated periodically requested according to the criteria of the attending gastroenterologist. Among them, at the beginning of the phase, a calprotectin should be performed, that is to say, a single stool sample should be submitted to the laboratory first thing in the morning. This laboratory result will tell us about the degree of intestinal inflammation at the time of collection.

Phase 2: 6 weeks. Patients in the case group will receive 75% of the calories calculated as a diet with recommended and prohibited foods for Crohn's disease and 25% of the calories calculated as a milk formula recommended for these diseases (MODULEN). You will have your usual check-ups with your primary gastroenterologist and will also have a joint interview with the nutritionist Lic. Betania Jauregui and Dr. Maria Soledad Arcucci who will guide you in the diet, perform a physical examination of the patient and

measure growth parameters such as weight and height. In addition, questions will be asked to evaluate symptoms associated with disease activity and laboratory results will be evaluated periodically according to the criteria of the attending gastroenterologist. Among them, at the end of the phase, a calprotectin should be performed as part of their usual controls.

Phase 3: Follow-up for 12 months from the beginning of the protocol. It will be evaluated by clinical history if during this period you presented relapses or changes in the treatment.

Throughout the study, you will be followed up by our team in the same way as usual.

Participation in the study is voluntary and free of charge. There are no financial benefits to participating in the study. This study will not result in additional expenses for you or your medical coverage.

The decision to participate or not, does not modify in any way the treatment received, nor the medical follow-up. Your primary care physician will be notified of your participation in the study.

How will I benefit from participating in this study?

You must understand that this is a research work developed and supervised by specialists of the service, who work daily in our institution and whose usual practices are reflected in this undertaking. The ultimate goal of this work is to improve medical practices, with the incorporation of new treatments based on methodologically developed clinical evidence.

You will not have a direct benefit from participating in this study, but the results of the study may allow future children and adolescents to benefit from a more rational and specific use of treatments for Crohn's disease.

Risks of the study

The diet is not a risky treatment since it covers all the nutritional requirements of the patients. The only risk is the lack of tolerance which in fact will be one of the objectives of our work.

Confidentiality

All your data included in this study are confidential and will be treated only by the researchers, to protect your identity and privacy, according to the Law 25326 by which you have the right to access your personal data without any cost, at least every six months, unless there is a genuine and reasonable interest. In addition, you have the right to request the rectification of your data. The National Directorate for the Protection of Personal Data, under the Agency for Access to Public Information, the controlling body of Law 25.326, is responsible for dealing with queries, complaints or claims filed in relation to any issue regarding the protection of personal data. For such purpose, it may be addressed to: Avenida Presidente General Julio Argentino Roca 710-CABA 2°floor, data personales@aaip.gob.ar, www.argentina.gob.ar/aaip. Likewise, the subject of the study has the right to have his/her personal data processed in the future if he/she decides to withdraw consent.

The handling of the information will be anonymized, so that you cannot be identified in the presentations or scientific publications of this study.

Withdrawal from the study

If the team of treating physicians or the investigators consider, according to medical criteria, that you present any additional risk by participating in the study, you will be withdrawn from the study and the reasons for this decision will be explained to you. Thereafter, the diagnostic and treatment sequences will be as usual for any patient with inflammatory bowel disease.

Termination of the study

You may decide to withdraw from the study at any time by simply informing your treating physicians or by contacting them as indicated below. If you withdraw from the study, your data will not be analyzed. The decision to withdraw from the study does not change the medical follow-up or treatment in any way. The team of doctors treating you may decide at any time to withdraw you from the study if they believe it is safer for your health.

In case of withdrawal from the study, the reasons will be duly explained and everything necessary will be done so that this does not affect your health.

Conflicts of interest

There are no conflicts of interest of the researchers nor any relationship with the pharmaceutical industry. This is a research work developed by physicians who seek to give you a better treatment every day.

Treatment for damages or complications

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Patient's first and last name. Number and type of document. Signature. Date and time

Witness's first and last name. Number and type of document. Signature. Date and time

Investigator's first and last name. Number and type of document. Signature. Date and time