Name:

Year: Class of 2012

Research topic: Carrageenan and its effect on Ulcerative Colitis

Research study title: No Carrageenan Study

Researcher:

Elective Dates: 03/26/12 – 04/6/12

Total Elective Credit: 4 weeks

Research Proposal

I. Developing a Hypothesis

This is a pre-established research study, which I have become a part of. It was started approximately 2 years ago by at UICMC and at the University of Chicago.

For the past 30 years, the common food additive carrageenan has been used to induce intestinal inflammation that resembles Ulcerative Colitis in animal studies. Specifically, carrageenan has been shown to activate an innate immunity pathway (mediated by TLR4, Bcl10, NFkB, and IL-8) and a reactive oxygen species (mediated by NFkB and IL-8). In these studies, this additive has induced intestinal lesions, including ulcerations, hemorrhage, polyps, and adenomas.

In the average Western diet, >100mg/day of carrageenan is consumed. With this level of consumption of a compound known to cause pro-inflammatory effects, it is important and relevant to consider how its consumption might influence development of human disease or affect the manifestations of existing disease.

In this study, we will determine if withdrawal of carrageenan from the diet impacts on the duration of remission in patients with ulcerative colitis.

II. Literature review to evaluate uniqueness of proposed hypothesis or study

Currently, there are no studies similar to the one we will be conducting, testing the effects of carrageenan consumption on human disease.

The following papers have dealt with the pro-inflammatory effects of carrageenan in animal studies:

1. Tobacman JK. Review of harmful gastrointestinal effects of carrageenan in animal experiments. Environ Health Perspect 2001; 109:983-994.
2. Food and Nutrition Board, National Research Council. Estimating distribution of daily intakes of Chrondrus extract (carrageenan); Committee on GRAS List Surve-Phase III. Appendix C. Washington, D.C.: National Academy of Sciences, 1976:1-7.
3. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Carrageenan. IARC Monogr Eval Carcinog Rik Hum 1983; 31:79-94.

4. Tobacman JK. Chapter 10 – Toxic consideration related to ingestion of carrageenan. In Reviews in Food and Nutrition Toxicity, Volume 1. Edited by VR Preedy and RR Watson. New York: Taylor & Francis, 2003, pp.204-209
5. Shah ZC, Huffman FG. Current availability and consumption of carrageenan-containing foods. Ecol Food Nutr 2003; 42:1-15

III. A priori statistical analysis or power analysis for clinical studies

Statistical analysis will occur when at least a total of 36 subjects are enrolled in the project (18 per experimental and control group).

Per the IRB protocol, a total of 36 subjects will achieve 80% power to detect a SCCAI (explained below) difference of 1.0 between the two groups. This is based on the assumption that the mean SCCAI score in the carrageenan-consuming group is at least 2 and the mean score in the carrageenan-free group is 1, with a standard-deviation of 1.0.

IV. Experimental Design

The study is a double blind study in which all participants will be on a no carrageenan diet. Half of the participants will be assigned randomly to receive placebo capsules and half will receive capsules that contain 100mg of carrageenan (less than anticipated in an average diet – 250mg).

All participants will need to meet the following requirements:

1. Over 18 years of age
2. Biopsy proven diagnosis of Ulcerative Colitis
3. In remission for at least one month
4. Required corticosteroids to go into remission
5. Able to make choices about what foods to eat
6. Not pregnant

On acceptance into the project, patients will come to the CRC for an initial visit consisting of completing HIPAA documentation, information about dietary restrictions, and giving a small stool sample and 30 cc blood sample.

Patients will then be monitored by the administration of phone surveys/clinical questionnaires every 2 weeks to see the progression of symptoms (or lack their of). At 3 month intervals, patients will receive another 3 month supply of capsules, along with either giving a stool and blood sample at the CRC or mailing us a stool sample (with provided proper packaging).

Patients agree to stay in the study for a maximum of 1 year or will be removed if their condition relapses. Also, they will be debriefed at the end of the study about whether they received placebo or carrageenan capsules.

V. Obtaining and collecting data and avoiding bias

Data is collected via 2 methods

1. Calprotectin (an inflammatory marker elevated in patients with UC) is measured in fecal samples
2. Progression of symptoms measured via answers to 2 clinical questionnaires
    a. Simple Clinical Colitis Activity Index (SCCAI)

b. Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

During the patient's initial visit at the CRC, a stool sample is taken to measure for calprotectin. Also, both surveys are administrated with their answers yielding a baseline score. The surveys measure parameters such as bowel frequency (day & night), urgency of defecation, blood in stool, and general well-being. The surveys have a sliding-scale format for answers with each answer having a point value. The total point value is used for comparison purposes/assessment of symptoms.

These surveys will be conducted over the phone by either the CRC or me (after being trained by the CRC) at an interval of 2 weeks. The answers (and associated point value) will be noted and compared with their baseline value. If an increase of 2 points occurs on two consecutive surveys, the patient is considered to be relapsing, and will be removed from the study.

Also, at 3 month intervals, the patient will be required either to visit the CRC, where a stool sample will be taken, or mail a stool sample to the CRC. These fecal samples will be analyzed for calprotectin levels and compared to the patient's baseline value.

Medical records of study participants, including results of laboratory tests ordered by the patient's personal physicians, will be reviewed at 3 month intervals. At 3, 6,9, and 12 months since study onset, an interm analysis of study data will be prepared and comparisons made between the groups.

Bias is being addressed by making this a double blind, randomized study. Debriefing of which patients received placebo pills vs carrageenan pills will be done when the entire study is completed.

A potential confounder is the possibility patients will not adhere to a no-carrageenan diet. We believe the experimental group and control group will have the same difficulty with this criterion. We will assess their ability by doing 24-hour diet recalls during each phone call or CRC visit. If we see that more than 2 items containing carrageenan are consumed during 2 consecutive 2 week intervals, they will be removed from the study.

VI. Presenting raw data and statistical analysis and writing data in manuscript form

Currently, 4 individuals have completed the study. 6 individuals are currently participating in the study. I will be working with the CRC to see the results of the former patients and those undergoing the project. I will also be working with [redacted] and possibly Dr. [redacted] when statistical analysis will be done. Currently, we have not achieved enough patients to start analyzing the data.

VII. Preparing or submitting for publication

When the necessary number of patients are enrolled, we will start writing up the project, with the intent of being published. I am currently discussing with [redacted] about working on an abstract for the project. Preparing for publication will be further discussed as the project is not at that stage currently.

VIII. Ethics

The project is an IRB approved study, with the IRB accepting the protocol approximately 2 years ago. Personally, I have undergone IRB approval and completed an online research-specific HIPAA module (certificates can be provided upon request).

An ethical dilemma presented by the study design is the potential induction of relapse in patients who are currently in remission. When patients are experiencing increase in symptoms (or subsequent increase in maintenance medications), they will be promptly removed from the study even before the 1 year period they originally signed up for. Specifically, if at the time of interval analysis, it is demonstrated by study investigators that there is a significant difference between the occurrence of relapse between the two groups, the study data will be reviewed by an external data monitor appointed by the CRC to consider early termination of the study.

Patients will be notified about HIPAA, their personal rights of participation, and the sharing of medical records during their initial enrollment visit at the CRC. All medical information will be maintained confidential and only discussed with the patient and the physicians/research assistants on the IRB protocol.