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

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Introduction:

Crohn's disease (CD) is part of the inflammatory bowel diseases(IBD) with increasing incidence worldwide. It is postulated to be multifactorial in cause, but in pediatrics, genetics and environmental exposure seem to be the main triggers. Pediatric-onset IBD is often more extensive and is associated with a more aggressive course requiring early immunomodulation. The cumulative risk of progression to complicated CD is similar to that of adults, but by virtue of early disease onset, children are more likely to require surgery upon reaching adulthood for disease management.

The use of new medications such as biologics have changed the natural history of the disease, inducing a rapid response and remission, but involve high costs and additional toxicity, presenting considerable adverse effects such as severe infections, malignant and autoimmune sequelae. (Ruemmele et al. 2014). Moreover an increasing number of patients face loss of response to one or more of these agents despite combination therapy with immune modulators, therapeutic drug monitoring and dose adjustments.Even though combination with immunomodulators is considered an effective option to increase the long-term therapeutic effect of biologics such as infliximab, there are serious complications associated with this approach, such as an increased risk of hepatosplenic T-cell lymphoma (Mackey et al., 2009). Having alternative therapeutics that can potentiate a remission in immunosuppressed patients are an unmet need, especially in the pediatric population for whom new biologics will not be available in the near future. (Sigall Boneh et al. 2017; Nguyen et al. 2015)

Thinking about the pathophysiology of the disease, anti-TNF (the most used biologics currently used in the pediatric population) control only one inflammatory

pathway leaving others active and thus there may be disease progression. In addition, with this treatment we are not treating the factor that induces inflammation: CD is probably caused by a sequence of events, in which the Western diet (environmental factor) drives changes in the intestine and intestinal lining such as decreased microbial diversity and dysbiosis, altered barrier function, formation of bacterial biofilms and bacterial translocation and activation of the immune system leading to a vicious cycle of inflammation. (Levine, Sigall Boneh, and Wine 2018). So if diet is one of the triggers of inflammation and disease progression, dietary treatment should improve outcomes over time, reducing the need for immunosuppressive treatments and their sequelae in addition to nutritional improvements(Triantafillidis et al. 2009).

Exclusive enteral nutrition (ENN) has been endorsed since 2014 by international guidelines for induction of remission in patients with mild to moderate luminal CD because of its excellent safety profile, with success rates between 60-80% that further favor the theory of diet as the axis of the pathogenesis of the disease.(Ashton, Gavin, and Beattie 2019).(Levine, Sigall Boneh, and Wine 2018), but its tolerance is difficult.(Levine et al. 2019). This is why multicenter studies have been advanced to evaluate the efficacy of partial enteral nutrition (PEN) plus a nutritionally adequate diet (among them Crohn`s Diet exclusion disease, CDED) with very good results in terms of tolerance and inclusion of remission around 70% as well as in patients with secondary loss of response to anti TNF(anti-tumor necrosis factor) treatment (Levine et al. 2019) (Sigall-Boneh et al. 2014) (Limketkai et al. 2019).

Patients often view diet as a vital component of their IBD management. Dietary modification is a common practice in patients for a variety of reasons, including relapse prevention.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.(Gu and Feagins 2020).

There is a growing need to replace invasive procedures with noninvasive markers to monitor the course of the disease. Several pediatric studies have shown that low fecal calprotectin levels [below 150 to 250 µg/g] correspond well with endoscopic remission and higher levels usually reflect ongoing intestinal inflammation. A recent study evaluated that those patients with a calprotectin result <250 µg/g and the absence of symptoms at 12 weeks (end of biologic induction) had a higher likelihood of sustained remission during the first year (van Rheenen et al. 2020). The GROWTH CD study, a multicenter study of 222 untreated pediatric CD patients followed for 52 weeks, demonstrated that patients with Pediatric Crohn's Disease Activity Index [PCDAI] >5 [p = 0.012], C-reactive protein [CRP] >20 mg/L [p = 0.019] and fecal calprotectin > 400 µg/g [p = 0.001] at week 12 after starting induction therapy had an increased risk of relapse and early surgery.

Another recent study in children with quiescent CD receiving maintenance therapy with infliximab, a calprotectin level >250 µg/g before each infusion was a reliable predictor of clinical relapse in the following 3 months. In contrast, a decrease in fecal calprotectin to <250 µg/g [which is the upper limit of the target range] could be considered a reliable indicator of treatment success. The closer the calprotectin value is to 50 µg/g, the higher the probability of complete endoscopic cure(van Rheenen et al. 2020).

Works such as that of (Strisciuglio et al. 2020) have found a significant association between adherence to specific diets and a low fecal calprotectin level (p = 0.027).

Currently in our service, according to international guidelines, patients who present severe inflammatory disease with severe activity or poor prognostic factors (deep colonic ulcers, marked growth retardation) or who present severe persistent disease after induction are started on biologic therapy. Once the induction with the selected biologic medication is completed, they are clinically monitored with

inflammatory markers and calprotectin in fecal matter, and according to the results, the need and time to perform a new endoscopy is evaluated. If calprotectin is elevated, generally higher than 300 ug/g, a new endoscopy is indicated.(Koninckx et al. 2021) However, when the only elevated value in isolation is calprotectin and clinically and endoscopically the patient presents favorable evolution, once the biologic is optimized there are not many therapeutic tools to offer and the evolution is usually observed, knowing that they will probably present relapses in the future. It is in this group where we believe that the diet can collaborate to their total remission and mucosal healing.

Due to the success of diet in achieving remission in mild-moderate forms of the disease, and an increasing number of patients with loss of response to available drugs despite increasing dosage and pathophysiology of the disease, the aim of the present study is to evaluate whether there is response with the addition of diet therapy in patients with moderate/severe CD who receive biologic therapy (infliximab or adalimumab) and present active disease. (Sigall Boneh et al. 2017)(Triantafillidis et al. 2009; Hartman et al. 2008).

General objective:

To evaluate the response to the addition of dietary therapy in CD patients with severe disease at debut or with poor prognostic factors on treatment with biologics, who after induction present at some point in their evolution calprotectin values greater than limit value (greater than 250 ug/g).

Specific objectives:

In CD patients on biologic treatment who after induction present at some point in their evolution calprotectin values greater than the limit value (>250 ug/g):

Compare the proportion of patients with normalization in calprotectin values (<250 ug/g) at 12 weeks with or without the addition of dietary therapy.

Evaluate calprotectin level at 0 and 12 weeks in patients with or without the addition of dietary therapy.

Assess tolerance to the diet in the treatment period: defined as adherence/ability to continue the diet and not drop out during at least the 12 weeks of the study.

To assess the number of relapses and treatment changes (need for intensification of biological treatment, need for steroids, immunosuppressants or surgery) during the first year with and without the addition of diet therapy. To compare the growth of patients by anthropometry with and without the addition of diet therapy.

Material and Methods:

Study design:

Multicenter randomized controlled intervention study.

Setting:

Hospital Italiano de Buenos Aires is a reference university center in Argentina, with an annual average of 10/15 patients diagnosed with pediatric IBD per year . We currently have about 30 patients with CD treated with anti-TNF therapy. Patients undergo periodic follow-up in the Pediatric Gastroenterology Service, then transition to the Adult Service, to which they are referred once the process is completed.

Period

The study is scheduled to start in May 2021. Patients will be invited to participate in the protocol for 12 weeks with pre-set consultations at weeks 0, 6 and 12. They will then continue their usual consultations with the service and will be evaluated one year after the start of the protocol by EHR. The total duration of the study is estimated to be 2 years.

Population

Patients under 18 years of age

With a diagnosis of CD

Who completed remission induction with biologic therapy

Who are on maintenance biologic therapy

and present calprotectin values greater than the laboratory established limits (greater than 250 ug/g).

Exclusion criteria

Children who are unable to receive the diet by enteral route.

Comorbidities affecting nutritional status and/or bone metabolism, growth or pubertal development.

Children already on special diets.

Proposed intervention:

All patients who meet the inclusion criteria and do not present exclusion criteria will be offered to enter the protocol and after signing informed consent, they will be informed about the possible interventions. They will

then be randomized into a DIET group and a NO DIET group.

Patients in the NO DIET group will continue with their usual treatment with biologics according to the usual practices and criteria of the treating physician.

Patients in the DIET group will receive CDED (Crohn's Diet Exclusion Disease) with NEP (partial enteral nutrition) 50% of the calculated calories, according to the recommended diet for the first 6 weeks and CDED with PEN (partial enteral nutrition) 25% for the following 6 weeks, they will also continue with their usual treatment with biologics according to the usual practices and criteria of the treating physician.

Patients will receive as NEP a polymeric formula made exclusively for patients with inflammatory diseases at 1 kcal/ml (Modulen, Nestlé, Switzerland). Patients will be able to contact the nutritionists by e-mail and receive a collection of recommended recipes compatible with the CDED that could be used to improve the palatability and variety of meals (Annex 1).

All patients in the DIET group will receive the same diet for 12 weeks.

Compliance will be assessed directly by questions from physicians and nutritionists (annex 1). Patients who cannot consume the full amount of the recommended formula or alternative formulas could reduce the dose, as long as they meet the nutritional requirements according to sex and age.
In all patients (DIET and NO DIET group) calprotectin levels will be measured at 12 weeks according to usual practice and will be monitored at 6 and 12 weeks according to usual practice.

Outcome Variable:

Proportion of patients with calprotectin normalization at 12 weeks 1: calprotectin normalization: less than 250ug/g , 0: calprotectin greater than

250 ug/g.

Calprotectin values at 0 and 12 weeks. Numerical variable Continuous

Tolerance to the diet for 12 weeks 1: yes 0 : no. To be evaluated by symptoms according to short PCDAI (annex 2).

Diet adherence: a 5-day feeding report will be requested prior to the consultation at weeks 6 and 12. The report will be evaluated by a nutritionist to verify food compliance, caloric/protein intake according to particular needs.

Number of relapses at 12 weeks and one year after the intervention: Numerical variable. Relapse is considered when the patient presents worsening of intestinal/extraintestinal symptomatology, elevated inflammatory parameters, endoscopy/pathological anatomy or imaging with active disease.

Need for changes in the basic treatment at 12 weeks and one year after the intervention 1: yes 0: no .
Growth assessment at 0, 12 weeks and 1 year after the intervention: weight, height and score according to the Guidelines (Guide for physical growth assessment, SAP 2013).

Our center does not have drug or antibody dosing for biological drug dosing.

Explanatory variables

Demographic characteristics

Date of diagnosis: according to EHR, the date of diagnosis will be the first pathological endoscopy.

Age in years at the time of evaluation. Continuous variable.

Sex: according to phenotypic sex. Dichotomous variable: 1: female 0: male.

Related to pathology

Location of the disease Categorical variable according to Montreal Classification: 1: ileal, 2: colonic, 3: ileocolonic or 4: combined with upper gastrointestinal involvement.

Duration of the disease: number of months between diagnosis and admission to the protocol. Numerical variable.

IBD treatment: at the time of protocol entry and at 12 weeks and 1 year. Non-exclusive categorical variable: 1: 5 ASA, 2: corticosteroids, 3 biologics (Infliximab, Adalimumab), 4 Nutrition, 5 surgery.
Disease activity: continuous variable according to pediatric Crohn's disease activity index(short PCDAI(Turner et al. 2012), appendix 2) at protocol entry and at weeks 6 and 12 and at 1 year. 1: remission less than 10, 2: mild disease 10-25 3: moderate 25-40 4: severe more than 40

Results of inflammatory markers at weeks 0, 12 and one year of protocol (calprotectin, albumin, CRP, ESR and hematocrit). Continuous variable

Nutritional status: anthropometry and z score according to national guidelines (Guide for the evaluation of physical growth, SAP 2013).

Data collection

Hospital Italiano has an Electronic Health Record (EHR) system, where clinical, laboratory and imaging data are recorded. The data will be obtained from the visits stipulated according to the protocol (0, 6 and 12 weeks) and will be entered in a card (Appendix 1) that will be used as a template for the EHR evolution.

Patients will be evaluated at each visit by a gastroenterologist and a nutritionist.

A database will be created in RedCap, coordinated by the researchers of the Hospital Italiano, where the data of the patients included in the study will be anonymized and coded (see ethical considerations section).

Sample size calculation

The sample size calculation is performed considering a calprotectin normalization

ratio in the diet group of 50% versus 10% in the control group (Sigall Boneh et al. 2017; Nguyen et al. 2015) for an alpha of 0.5 and a power of 80% a total of 40 patients are required(20 per group).Considering a loss of 20% 24 patients per group will be included. The sample calculation was performed using STATA 13 software for MAC.

Inclusion, evaluation and follow-up

Sampling will be consecutive. All patients who meet the inclusion and not exclusion criteria will be invited to participate in the study and, after signing the informed consent form, they will be randomly assigned to one of the two treatment arms.

This assignment will be made by generating a randomization table by blocks associating the treatment assigned to each patient number included. This assignment will be kept in sealed envelopes for each patient until the time of patient inclusion.

Statistical analysis:

The analysis will be performed per protocol and by intention-to-treat. The unit of analysis will be each patient within one of the two treatment branches.

In the descriptive analysis, quantitative variables are expressed as mean and standard deviation or median and interquartile range according to the observed distribution. Categorical variables are expressed in proportion with relative

frequency and absolute frequency.

The association between the outcome variables and the assigned treatment branch will be evaluated with Chi-square test for dichotomous results and with t test or Mann Whitney test for quantitative results. ORs with their 95% CI will be reported. The confounding effect of the variables will be tested with logistic regression or linear regression model as appropriate. A probability of less than 5% will be considered statistically significant. The analysis will be performed with the statistical software package STATA13 for MAC.

Adverse Events

Adverse events will be collected during each control and each time the patient contacts the investigator. They will be classified according to their severity according to the investigator's experience they will be classified as: Mild, Moderate and Severe:

1. Mild are those that are transitory, do not require special treatment and do not interfere with the patient's daily activities.

Moderate are those that cause a low level of inconvenience or concern to the patient and may interfere with daily activities, but which respond to simple therapeutic measures.

3. Severe are those that disrupt the patient's daily activity and require systemic treatment with drugs or other treatment. Severe adverse events are all those that lead to death, hospitalization or threat to life.

Clinical Management and Study Withdrawal

The patient may withdraw from the study at any time by informing the investigators.

If the team of treating physicians or the investigators consider, according to medical criteria, that the patient presents any additional risk by participating in the

study, the patient will be withdrawn and the reasons for this decision will be explained.

In addition, patients will be withdrawn from the study if during the treatment they present a nutritional deterioration that requires another type of intervention or if during the protocol the enteral route is contraindicated for any reason.

Ethical considerations

The right not to participate in the study will be respected at all times, without this implying in any case any type of discrimination, differential treatment or mistreatment.

The proposed intervention only contemplates the addition of a specific diet to the usual treatment. No invasive procedures or changes in pharmacological treatment beyond the usual practice will be performed, so no complications related to the protocol are expected.

The present study will be carried out respecting the considerations related to the care of clinical research participants included in the Declaration of Helsinki and in accordance with the Guidelines for Research in Human Health (Resolution 1480/11) of the National Ministry of Health. All the information will be obtained from the EHR and will be used by the researchers with the strictest confidentiality, taking into account the details of Law 25.326 on data protection. For this purpose, each patient will be registered with a consecutive number in a database to which only the principal investigator and the sub-investigators will have access.
To keep the information secure, the principal investigator and the sub-investigators of the Hospital Italiano will have a codified list of the patients included in their center, under security norms and only with access by them. This list will be used to identify patients and complete the RedCap database. The same methodology will be applied by the other participating centers.

In the event of any doubts arising at the time of data verification or analysis, the coordinating center will ask each participating center to review the data, using the patient code entered in the database. With this code, the investigators of the participating centers will be able to review what was requested by the coordinating center without jeopardizing the identity of the research subjects.

The legal guardians of the patients will sign an informed consent form to participate in the study and in those children over 14 years of age, their consent will also be requested.

The protocol has been developed with advice from the Research Department.

Funding

The administrative expenses of the study will be financed by the pediatric gastroenterology service.

The milk formula will be requested to the patient's coverage as part of his treatment for his underlying pathology, which is routinely requested to the coverage in our service, since according to the recommendations of the ESPEN guidelines, polymeric enteral nutrition of moderate fat content can be used as primary nutritional therapy and support in active IBD (recommendation 18) (Bischoff et al. 2020) and in published research such as that of Hartman (Hartman et al. 2008) where Modulen IBD was used in addition to conventional treatment, showed an improvement in the remission of the disease and in the body mass index of the patients.

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Annex 1

Patient no:

Week: ⇖ OR ⇖6 ⇖12 ⇖Year.

Group ⇖Diet plus biologic ⇖Biologic

Date of diagnosis

Age

Sex

Location of disease

⇖ ileal ⇖ colonic ⇖ ileo colonic ⇖ combined with upper gastrointestinal involvement.

Relapses between this and previous evaluation ⇖Yes n°__ ⇖No. Current treatment ⇖ 5 oral or topical ASA ⇖ oral corticosteroids, topical or ev ⇖ Infliximab ⇖ Adalimumab)

Dose of infliximab/ adalimumab: ___ mg/kg.

Frequency of biologic administration: ⇖ weekly ⇖every 2 weeks ⇖every 3 weeks ⇖every 4 weeks ⇖every 6 weeks ⇖ other:___.

Short PCDAI : ⇖ less than 10 ⇖ 10-25 ⇖ 25-40 ⇖ more than 40

Laboratory

Hematocrit ____%

Calprotectin __ ug/g

Albumin ____ g/dl

CRP ____ mg/L

ERS ___ mm

Nutritional status: Weight:_____ kg z score:____ Height____ z score: ___

BMI: ____ growth rate:____

For the Diet plus biological group:

Amount of modulen per day: _____ ml

Bring report ⇖Yes ⇖ No

How difficult was it to perform the diet?

Score from 1(minimum)-10(maximum) ____

How similar is it to your usual diet?

Score from 1(minimum)-10(maximum): ___

Annex 2- short PCDAI:

In the week prior to consultation you presented with:

Abdominal pain

⇖No

⇖ Mild (short, does not interfere with activities)

⇖Moderate/severe(all day, lasted a long time, affected usual activity, nocturnal).

General well-being.

⇖No activity limitation.

⇖ Occasional difficulty in maintaining age-appropriate activities.

⇖Frequent activity limitations.

Daily catharsis

⇖0-1, liquid, bloodless

⇖ up to 2 semiformed with little blood or 2-5 liquid.

⇖Significant bleeding or greater than or equal to 6 liquids or nocturnal diarrhea.

Physical examination

Age---

Current weight and 1 year ago ---/----

Current height and 1 year ago ---/---/---

Abdomen

⇖- No mass or tenderness

⇖ Local mass or tenderness

⇖Sensitivity, defensiveness, well-defined mass.

Perianal disease

⇖No, skin tags

⇖ 1-2 asymptomatic fistulas

⇖Active fistula, draining or abscess.

Extraintestinal manifestations

⇖Fever

⇖Arthritis

⇖Uveitis

⇖Erythema nodosum

⇖Pioderma Gangrenosum