Nutritional Supplementation with Polymeric Diet Enriched with Transforming Growth Factor-Beta 2 for Children with Crohn's Disease

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Key words: Crohn's disease, nutritional therapy, transforming growth factor-beta, children

Abstract

Background: A polymeric diet rich in transforming growth factor-beta 2 used as a single nutrient has been shown to induce remission in 79% of children with Crohn's disease.

Objectives: To summarize the experience of several pediatric gastroenterology units in Israel using a TGFβ2-enriched polymeric diet (Modulen IBD®) supplementation in children and adolescents with Crohn's disease.

Methods: In a retrospective study we reviewed the charts of 28 children with Crohn's disease (10 girls, 18 boys) who received, in addition to conventional treatment, Modulen IBD as a supplement to their regular nutrition. These children were compared with 18 children supplemented with standard polymeric formula (Ensure Plus®) and 18 children without formula supplementation. We recorded clinical manifestations, growth, and the Pediatric Crohn's Disease Activity Index before and after initiation of the polymeric diet.

Results: The Modulen-treated children showed a significant decrease in PCDAI from 34.3 to 15.7 ($P < 0.0001$). A significant decrease in PCDAI was recorded also in the Ensure Plus group, from 35 to 22 ($P = 0.02$) but not in the non-supplemented group. Significant improvements in body mass index ($P = 0.01$) and erythrocyte sedimentation rate ($P = 0.03$) were recorded at follow-up (median 3.4 months) only in the Modulen IBD group.

Conclusions: In this cohort of children with Crohn's disease, supplementation of the diet with Modulen IBD as well as supplementation with Ensure Plus was associated with a decrease in PCDAI. The children supplemented with Modulen IBD also showed improvement in BMI, suggesting an additional advantage of nutritional therapy in children with this disease.

IMAJ 2008;10:503–507

Crohn's disease is a chronic, relapsing inflammatory disease of the gastrointestinal tract commonly diagnosed in childhood and adolescence. Malnutrition and growth impairment are significant complications of inflammatory bowel disease in pediatric patients [1]. Although the etiology of growth failure is multifactorial, the two major etiologic factors are chronic undernutrition and the direct effects of inflammatory mediators secreted from the inflamed gut [2]. Treating the intestinal inflammation and providing adequate nutrition are essential to prevent or remedy growth impairment. In addition, enteral diets – both elemental and polymeric – used as primary therapy in Crohn's disease have been shown to induce disease remission without concomitant use of other medications [3,4]. Furthermore, supplementary enteral nutrition after primary therapy and after remission is induced may be associated with the prolongation of remission and promotion of linear growth [5-8]. The pathways by which enteral diets may affect mucosal inflammation are manifold. Practically, there is evidence that an enteral diet has a direct effect on the gut mucosa by reducing cytokine production and the accompanying inflammation [9,10]. Modifications of the enteral diet composition have been evaluated in many studies. Such modifications include changes in fat and protein content and type and the addition of bioactive peptides [11,12]. The addition of bioactive peptides to enteral diet formulas may contribute by means of their specific growth factor effects or anti-inflammatory actions.

Transforming growth factors-beta are multifunctional key regulatory peptides that are produced by, and act on, a host of different cell types. Three isoforms (TGFβ1, 2 and 3) and three receptors (types I, II and III), with which all isoforms interact, have been identified in mammals. TGFβ is best known for its effect on cell growth and differentiation and immunoregulation. Like many cytokines in the intestinal tissue, it can act in autocrine and paracrine fashion and controls the differentiation, proliferation and activation state of lymphocytes, macrophages and dendritic cells, and as such plays a critical role in mechanisms of tolerance, prevention of autoimmunity and in anti-inflammatory processes [13].

TGF-β2 = transforming growth factor-β2
PCDAI = Pediatric Crohn's Disease Activity Index
BMI = body mass index

Based on the known anti-inflammatory and healing properties of TGFβ, it was reasonable to assume that a polymeric diet containing TGFβ may be of clinical value. To date three cohort studies have examined the value of a TGFβ-enriched formula in patients with Crohn's disease [14-16]. In all three studies the patients received the TGFβ diet for 8 weeks as their sole nutrition, followed by a 4 week period of controlled reintroduction of normal food. The TGFβ diet was effective in inducing remission and mucosal healing. Biochemical markers of inflammation, erythrocyte sedimentation rate and C-reactive protein levels normalized and serum albumin levels improved significantly. Endoscopic examination revealed a significant improvement also in the appearance and histology of the mucosal tissue. In addition, there was a reduction in the mRNA levels for the pro-inflammatory cytokines interleukin-1β, IL-8 and interferon-gamma [15].

Exclusive enteral nutrition is hard to implement in practice. Not only does it require a high degree of motivation on the part of the patient, but low palatalability, high cost and the need to insert a nasogastric tube are additional reasons to decline exclusive formula feeding for children and adolescents with Crohn's disease. Modulen IBD® (Nestle, Vevey, Switzerland) is an oral polymeric diet rich in TGFβ. For the last 3 years it has been our practice to administer Modulen IBD as a nutritional supplement to the regular diet of all children with active Crohn's (newly diagnosed or disease relapse), in addition to appropriate medical therapy. In this retrospective study we report the experience of several pediatric gastroenterology and nutrition units in Israel regarding the effects of nutritional supplementation with Modulen IBD on disease manifestations and activity. This group of patients was compared with a historical group of patients with Crohn's disease matched for age and disease severity who were supplemented with conventional formula, and with patients who received drug treatment as the sole therapy.

Patients and Methods

The medical files of 28 children and adolescents with Crohn's disease (10 girls, 18 boys), aged 13.1 ± 4.1 years (median 14 years, range 5–20) were retrospectively reviewed. The disease had been diagnosed based on the combination of clinical features and characteristic radiological, endoscopic and histological criteria at age 10.7 ± 3.3 years (median 11.3 years, range 5–16). The patients were followed at six major pediatric gastroenterology and nutrition units in Israel.

These patients were compared with two historical groups of patients. The first group comprised 18 children (7 girls, 11 boys) aged 12.71 ± 2.3 years (median 12.9 years, range 10–16.1) with Crohn's and matched disease severity who had been supplemented with a conventional formula before the advent of Modulen IBD. The second group included 18 children (10 girls, 8 boys) aged 13.3 ± 2 years (median 12.8 years, range 9.7–17) with Crohn's disease treated during the same period who had refused any form of nutritional supplementation. All these patients were diagnosed and followed at the Pediatric Gastroenterology and Nutrition Unit, Meyer Children's Hospital, Haifa.

The following data were retrieved from the medical charts: demographic information, disease manifestations and localization at the diagnosis and at the start of nutritional supplementation, and the amount and duration of Modulen IBD or conventional formula supplementation. The type of medication, Pediatric Crohn's Disease Activity Index [17], anthropometric data (weight, height and body mass index z-scores) and laboratory tests (ESR, hematocrit, albumin) at the start and at follow-up were also recorded. Disease activity was estimated as follows: severe disease (PCDAI > 30), moderate (PCDAI 15–30), remission (PCDAI < 15). In addition to data on patients treated with Modulen IBD, each pediatric gastroenterologist was asked to provide information on the number of patients with inflammatory bowel disease under his or her care, the number of patients to whom Modulen IBD was recommended, and the reasons for not using Modulen IBD.

Modulen IBD is a polymeric diet with casein as its protein source, which is rich in TGFβ2 (> 24 ppm). The protein content is 14%, the carbohydrate content 43% and the fat content 41%. It is lactose free, with glucose polymers and sucrose as the carbohydrate sources. Its lipid content is made up of milk fat (56%), corn oil (15%) and medium chain triglycerides (25%). The caloric density of the feed is 1 kcal/ml with an osmolarity of 370 mosm/L and has been formulated to contain adequate amounts of vitamins, minerals and trace elements. The standard formula used for nutritional supplementation was Ensure Plus® (Abbot Laboratories, Abbott Park, IL, USA), a lactose-free polymeric diet with casein as its main protein source. The protein content of this formula is 14.6%, the carbohydrate content 56.4% and the fat content 29%. The caloric density of the feed is 1.5 kcal/ml with an osmolarity of 680 mosm/L and it contains 100% of the U.S. recommended daily allowance for vitamins, minerals and trace elements. A nutritional supplement, Modulen IBD or Ensure Plus, was given in addition to a normal diet to provide 35–50% of total caloric intake.

Statistical analysis

Statistical analyses were performed using the SPSS statistical program, version 11.0 (SPSS, Chicago, IL). The results for continuous variables are given as mean ± SD, with the range. The results for non-continuous variables are given as frequency and percentage. Data at baseline and at follow-up were compared with the use of a Wilcoxon signed-rank test for matched pairs. To determine factors that were predictive of improvement at follow-up, we used the Wilcoxon test for categorical variables (gender) and the Spearman correlation coefficient for quantitative variables (age, duration of treatment, PCDAI). All statistical tests were two-tailed. *P* values less than 0.05 were considered statistically significant.

Results

Eight pediatric gastroenterology specialists provided data for 38 patients with Crohn's disease treated with Modulen IBD between January 2002 and December 2004. That represents about 10% of the total number of patients with Crohn's treated by these

IL = interleukin
ESR = erythrocyte sedimentation rate

physicians. Modulen IBD was recommended to about 100 of these patients but about two-thirds of them declined nutritional supplementation for various reasons: bad taste, high price, intolerance, or no reason at all. Six patients who had been treated with Modulen IBD as the sole nutrition and four patients without sufficient data were not included in the analysis.

Table 1. Demographic data and disease characteristics at the start of nutritional supplementation and in the control group

	Modulen IBD supplementation group (n=28)	Ensure Plus supplementation group (n=18)	Non-supplemented group (n=18)
Age at diagnosis (yrs)	10.7 ± 3.3	11.9 ± 2.4	11.9 ± 2
Age at inclusion in the study (yrs)	13.5 ± 4.1	12.7 ± 2.3	13.3 ± 2
Disease manifestations			
Abdominal pain	20/28	10/18	8/18
Diarrhea	19/28	12/18	10/18
Weight loss	13/28	8/18	7/18
Growth retardation	8/28	5/18	6/18
Other (anemia, arthritis, perianal disease)	9/28	9/18	6/18
Disease localization			
Upper GI tract and small bowel	5/28	4/18	3/18
Small bowel and colonic disease	15/28	12/18	10/18
Colonic disease only	8/28	2/18	5/18
Presence of low weight (weight z-score < -2SDS)	18/28	10/18	9/18
Presence of short stature (height z-score < -2SDS)	11/28	5/18	6/18
Quantity of formula consumed (ml/day)	700 ± 300	690 ± 270	–
Duration of nutritional supplementation or follow-up (mos)	5.3 ± 5	4.5 ± 2.6	5.5 ± 2.5

The demographic and disease characteristics at the initial evaluation are summarized in Table 1. There were no differences with regard to age, disease manifestations, localization, or the presence of low weight and short stature at the start of nutritional supplementation. Furthermore, the daily quantities of formula and the duration of supplementation were similar in the supplemented groups. Six children in the Modulen IBD group and five in the Ensure Plus group required a nasogastric tube, and one had a gastrostomy inserted; others managed to take their nutritional supplement orally. All patients were followed as ambulatory patients. Some minor symptoms attributed to both treatments were reported, namely nausea in two cases and diarrhea with abdominal pain at the start in three cases. These symptoms subsided shortly thereafter.

Table 2 shows the PCDAI, anthropometric data, the results of laboratory tests and the type of medication in all children at the start of nutritional supplementation and at follow-up. The severity of the disease, as assessed by PCDAI, was similar in the three groups before the start of nutritional therapy. Children supplemented with Modulen IBD had a significant decline in PCDAI at follow-up, from 35 ± 17 to 15 ± 13 (P = 0.0001). Children in the Ensure Plus supplemented group also showed a significant decrease in PCDAI, from 31 ± 11 to 22 ± 7 (P = 0.02), although less so than the Modulen IBD group, whereas PCDAI in the non-supplemented group did not change significantly. At follow-up, PCDAI in the Modulen IBD group was not significantly different compared to the Ensure Plus group, but was significantly lower than in the non-supplemented group (15 ± 13 vs. 21 ± 12, P = 0.04). In contrast, PCDAI of the Ensure Plus group at follow-up was not significantly different from the PCADI in the non-supplemented group. PCDAI

Table 2. Changes in disease activity, anthropometry, laboratory tests and medications during nutritional supplementation and follow-up

	Modulen IBD supplementation group (n=28)		Ensure Plus supplementation group (n=18)		Non-supplemented group (n=18)	
	Start of Modulen IBD	Follow-up	Start of Ensure®	Follow-up	Start of follow-up	Follow up
PCDAI (mean ± SD)	35 ± 17	15 ± 13[a]	31 ± 11	22 ± 7[b]	27 ± 10	21 ± 12
Disease severity						
Severe, PCDAI > 30	14/28	4/28[c]	9/18	4/18	7/18	4/18
Moderate, PCDAI 15–30	12/28	8/28	6/18	10/18	11/18	10/18
Remission, PCDAI < 15	2/28	16/28[a]	3/18	4/18[d]	0/18	4/18[d]
Anthropometric data						
Weight z-score (mean ± SD)	-1.7 ± 1.4	-1.1 ± 1.3	-1.8 ± 1.1	-1.2 ± 0.9	-1.2 ± 1.6	-1 ± 1.4
Height z-score (mean ± SD)	-1.2 ± 1.4	-1 ± 1.2	-1 ± 0.9	-0.9 ± 0.9	-1 ± 1.1	-1 ± 1
BMI z-score (mean ± SD)	-1.3 ± 0.8	-0.7 ± 0.7[e]	-1.8 ± 1.9	-0.9 ± 1	-0.8 ± 1.5	-0.6 ± 1.3
Laboratory tests						
ESR (mm/hr) (mean ± SD)	33 ± 17	22 ± 17d	33 ± 15	25 ± 10	32 ± 17	26 ± 19
Hematocrit, (mean± SD)	34 ± 4	37 ± 4	32 ± 3	34 ± 3	35 ± 3	35 ± 2
Albumin (g/dl) (mean ± SD)	3.6 ± 0.5	3.9 ± 0.5	3.6 ± 0.4	3.8 ± 0.3	3.7 ± 0.4	3.8 ± 0.3
Medical therapy						
5-aminosalycilic acid compounds	16/28	19/28	18/18	18/18	16/18	14/18
6-mercaptopurine	8/28	17/28d	2/18	4/18[e]	0/18	4/18[e]
Steroids	13/28	7/28	2/18	0/18	4/18	0/18
Infliximab	4/28	4/28	0/18	0/18	0/18	0/18
Antibiotics	4/28	0/28	2/18	0/18	0/18	018

[a]0.0001, [b]0.02, [c]0.009, [d]0.03, [e]0.01

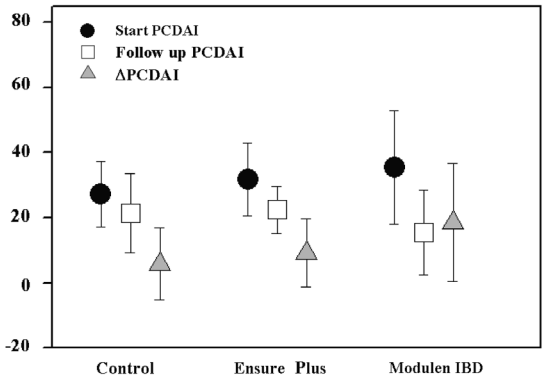

Figure 1. Means and SD for PCDAI scores at the start and follow-up and ΔPCDAI in the Modulen IBD, Ensure Plus and non-supplemented groups

score decreased during nutritional supplementation (ΔPCDAI) by 18 ± 18 points in the Modulen IBD group, 9 ± 10 points in the Ensure Plus group and 8 ± 11 points in the non-supplemented group. Comparison of ΔPCDAI between the three groups showed that the Modulen IBD group had a significantly greater decline in PCDAI as compared to the non-supplemented group only (P = 0.02) [Figure 1]. Improvement in the PCDAI (ΔPCDAI) correlated with disease severity (higher pretreatment PCDAI), r = 0.716, P = 0.001, but not with any of the variables studied (age, gender, disease manifestations or localization, type of medication, or type of nutritional supplementation). Significantly fewer children had severe disease in the Modulen IBD group at follow-up (4/28 at follow-up vs. 14/28 at study entry, P = 0.009) and significantly more children achieved remission (16/28 at follow-up vs. 2/28 at study entry, P = 0.0001). Furthermore, significantly more children attained remission in the Modulen IBD group as compared to both the Ensure Plus group and the non-supplemented group (P = 0.03). Anthropometric characteristics of the participants, as summarized by z-scores of weight, height and BMI and the laboratory tests were not different between the three groups, neither at the start of nutritional supplementation nor after [Table 2]. However, only the children in the Modulen IBD group had a significant improvement in BMI and ESR at follow-up.

Discussion

The results of this study suggest that nutritional supplementation with Modulen IBD in children with exacerbation of Crohn's disease may help to induce and maintain remission for the short term. In this retrospective analysis we found that the clinical response, reflected by the significant decline in PCDAI score, was associated with significant improvement in BMI and inflammatory markers. Children supplemented with the other formula (Ensure Plus) also exhibited a significant decline in PCDAI, but without significant improvement in nutritional status or ESR. Moreover, compared with the non-supplemented group, only children in the Modulen IBD group showed a significant decline in disease severity score.

Enteral nutrition is effective in inducing remission in active Crohn's disease [18]. However, its role in preventing relapses during periods of remission has not been explored widely [5]. Verma and colleagues [8] reported the successful use in adults of long-term enteral nutritional supplementation in maintaining remission and complete withdrawal of steroids in about half of the patients with steroid-dependent Crohn's disease. This may be particularly relevant in the pediatric population in whom steroid use may be associated with worrisome complications. Three studies in children assessed the role of prolonged supplementation with liquid diets in the maintenance of remission and in growth improvement. The results of these studies suggest that supplementary enteral nutrition without restriction of a normal diet was associated with prolongation of remission and improved linear growth [5-7]. There is no clear consensus as to which dietary therapy is best. Elemental diets do not seem to be superior to polymeric whole protein-based diets, although further research is needed on this subject.

Modulen IBD is a polymeric formula enriched in TGFβ2. The presence of TGFβ2 in enteral diets offers a means to antagonize the production and action of pro-inflammatory cytokines or chemokines in the intestinal mucosa. The concomitant overexpression of TGFβ and its signaling receptors in Crohn's disease points to a potential role of these regulatory molecules in the pathophysiology of the disease [19]. Studies in murine models have provided irrefutable evidence that eliminating TGFβ or disrupting its downstream signaling cascade leads to inflammatory disease [20]. Activation of TGFβ-mediated pathways might promote the repair of mucosal injury by enhancing the process of re-epithelization and extracellular matrix regeneration [21].

The use of Modulen IBD as a single nutrient has been shown in three uncontrolled studies to induce remission in most children with active Crohn's disease; however, the relapse rate was high after remission achieved with nutritional therapy [14-16]. Consequently, nutritional therapy is regarded today as a bridge until the effect of immunosuppressive therapy (usually 6-mercaptopurine) is achieved. The difficulties in carrying out nutritional supplementation with liquid formulas are reflected by the fact that only one-third of the children to whom Modulen IBD was recommended accepted this modality. Because of low compliance, 6 to 8 weeks of liquid diet as the single nutrient source are very hard to implement; therefore, we were compelled to devise some compromise and offer an enteral diet only as a supplement to standard nutrition. So far, no study addressing the role of Modulen IBD as adjuvant therapy in achieving and maintaining remission in Crohn's disease has been published.

In the current study, half of the children in the Modulen IBD group had severe disease and the rest had moderate disease severity. The PCDAI was remarkably improved and disease remission was achieved in more than half of the children, in association with significant change in BMI z-score and ESR. The introduction of new medication (6-MP) during Modulen IBD supplementation raises some reservations as to whether disease improvement was only the result of nutritional supplementation with Modulen IBD.

6-MP = 6-mercaptopurine

Furthermore, 6-MP was begun in most children during Modulen IBD treatment and it is known that there is a lag period of 3 to 6 months until the effect of 6-MP is noticed. Similar numbers of children were on infliximab at the beginning and the end of follow-up. Nevertheless, a separate analysis showed that similar improvement in PCDAI was present independent of whether new immunomodulatory medication was introduced or not.

In summary, this is the first study to analyze the role of Modulen IBD as long-term nutritional supplementation in patients with severe to moderate Crohn's disease and growth impairment. In this small cohort, dietary supplementation with TGFβ2-enriched polymeric formula helped to alleviate symptoms and decrease PCDAI, suggesting that this formula may lead to induction and maintenance of disease remission. The use of a conventional formula was also associated with a reduction in disease activity, although of less magnitude than with Modulen IBD supplementation. These results should be regarded with caution because of the limitations of the study: namely, it was retrospective, the number of patients was small and they came from different clinics, and historical controls were used for comparison. Patients with Crohn's disease typically relapse in the long term, irrespective of the therapeutic approach, therefore maintenance and retreatment strategies including prolonged nutritional supplementation should be more fully investigated, and the differences in the efficacy of the various formulae used in the nutritional supplementation in this disease should be prospectively evaluated.

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We should try to be the parents of our future rather than the offspring of our past

Miguel de Unamuno (1864-1936), Spanish writer and philosopher