

REGULAR ARTICLE

Does cow's milk protein elimination diet have a role on induction and maintenance of remission in children with ulcerative colitis?

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Keywords

Cow's milk protein, Diet, Inflammatory bowel disease, Pediatrics, Ulcerative colitis

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Received

12 December 2012; revised 11 February 2013; accepted 20 February 2013.

DOI:10.1111/apa.12215

ABSTRACT

Aim: Aims of this study were to evaluate the efficacy of a cow's milk protein (CMP) elimination diet on induction and maintenance of remission and to define association with atopy in children with ulcerative colitis (UC).

Methods: Twenty-nine consecutive patients (mean age: 11.2 years; range: 4.6–17 years; F/M: 15/14) with newly diagnosed UC were randomized either to receive a CMP elimination diet ($n = 14$) or to continue a free diet ($n = 15$) associated with concomitant steroid induction and mesalazine maintenance treatment. Children were prospectively evaluated at four time points: within 1 month, 6 months and 1 year after diagnosis or at the time of relapse.

Results: Twenty-five of the 29 enrolled patients responded to the UC induction therapy with a complete remission (86.2%), 13 belonging to CMP elimination diet group and 12 to free diet group ($p = 0.59$). Overall, our data showed that 7 of 13 (53.8%) patients treated with CMP elimination diet and 8 of 15 (53.3%) patients on free diet and UC therapy relapsed within 1 year of follow-up ($p = 1$).

Conclusions: In conclusion, data of this paediatric, randomized trial suggest that CMP elimination has no role in the management of UC in non-sensitized children.

INTRODUCTION

Food sensitivity/intolerance has been suggested to play a role in the aetiology of IBD, and the culpable foods vary on an individual basis. The foods excluded have been predominantly cereals, dairy products, yeast and certain types of fat (1). In particular, children with IBD often avoid dairy products more than they would need to, based on the prevalence of lactose malabsorption and/or allergy to milk proteins because of arbitrary advice from physicians. In a study by Jowett et al., 68% of UC adult patients believed that diet influenced their disease and modified their diet accordingly. The most common behaviour resulted the avoidance of milk and dairy products; this dietary change resulted in reduced calcium intakes but had no apparent effect on the rate of relapse (2). On the other hand, malnutrition is very common in children with IBD (3). At the time of diagnosis, up to 85% of paediatric patients with CD and 65% of patients with UC have weight loss (4). Unnecessary dietary exclusions are a concern if initiated without appropriate nutritional or medical supervision, given the importance of adequate calcium and vitamin D intakes in the prevention of osteoporosis in IBD (5). The origins of malnutrition in IBD are multifactorial, but dietary restrictions (due to intolerance of diet or therapeutic fasting) are considered to be relevant (6). Without further evidences, and considering the nutritional issues, it remains unclear whether dietary manipulation will continue to have

a role solely in symptom control, or whether complete remission may be possible using these methods in combination with pharmacological agents.

The purposes of this study were to evaluate the efficacy of a cow's milk protein (CMP) elimination diet on induction and maintenance of remission and to define the association with atopy in children with ulcerative colitis (UC).

METHODS

This was a prospective, single-centre, randomized, controlled, 1-year study of children with newly diagnosed UC consecutively enrolled at the Department of Translational Medical Sciences, Section of Pediatrics, University of Naples 'Federico II', Italy. Twenty-nine consecutive patients (mean age: 11.2 years; range: 4.6–17 years; F/M:

Key notes

- Allergy to milk protein has been reported to play a possible role in the etiopathogenesis of UC.
- Unnecessary dietary exclusions are a concern if initiated without appropriate nutritional or medical supervision.
- Data of this paediatric, randomized trial suggest that cow's milk protein elimination diet does not modify the time of induction and the risk of relapse.

15/14) with newly diagnosed UC, based on accepted historical, endoscopic, histological and/or radiological criteria (7), were randomized either to receive a CMP elimination diet ($n = 14$) or to continue a free diet ($n = 15$).

All patients with a Pediatric Ulcerative Colitis Activity Index (PUCAI) score ≥ 35 received concomitant steroid induction treatment (oral methylprednisolon: 1 mg/kg/day, maximum 40 mg/day per 4 weeks) and oral mesalazine induction and mesalazine maintenance treatment (50 mg/kg/day), while subjects with a PUCAI score <35 received exclusively oral mesalazine induction and mesalazine maintenance treatment (50 mg/kg/day). The paediatric gastroenterologists (AS; EM) made all decisions regarding induction therapeutic intervention being unaware of diet group allocation. A detailed list of food containing milk proteins was given to each patient to avoid them during the elimination diet period. During the study period, parents and/or patients were asked to record in a daily diary only the amount and type of not allowed food. At the end of the study, these diaries were analysed to evaluate adherence to the diet and the quantity of milk consumed. The parents were able to contact one of the investigators (MM) whenever necessary, and frequent telephone contacts helped to ensure adherence to the diet. All children received supplemental elemental calcium 1000 mg/day and vitamin D3 0.25 mcg/day for 1 year. Exclusion criteria were children who had received therapy-inducing remission of UC and/or children who required surgery for complications related to UC.

Assignment to CMP elimination diet or free diet was determined according to a computer-generated randomization scheme. Excellent compliance was defined as no violation of the protocol with respect to the intake of the diet.

After 4 weeks, patients who were in remission began tapering off corticosteroids on a weekly basis (25%/week) on the basis of the PUCAI score. Upon induction of remission patients continued to receive concomitant therapy (CMP elimination diet group: mesalazine and CMP elimination diet; free diet group: mesalazine and free diet) for 1 year or until relapse.

Additional information collected at the first visit included demographic data, family history and symptom onset. At diagnosis, physical examination was performed by a paediatrician and included an abdominal examination and evaluation of extraintestinal manifestations of UC. Age- and gender-specific z-scores (standard deviation scores) for height and weight were calculated using National Center for Health Statistics 2000 Center for Disease Control data.

The PUCAI and physician global assessment (PGA) were used to measure disease activity (8). The extension of disease involvement was evaluated using the Paris Classification (9). Clinical remission was defined on the basis of PUCAI < 10 , while clinical response to the induction treatment was identified as a PUCAI score a change of at least 20 points from baseline. Clinical relapse was defined as the occurrence or worsening of symptoms accompanied by an increase of PUCAI >10 points, sufficient to require

rescue treatment with corticosteroids, azathioprine/immunosuppressive agents, or surgery. When a relapse occurred, the study protocol was stopped and the patient was treated according to the physician's preference. Laboratory studies including complete blood count, albumin, ESR, CRP, calcium and phosphorus were performed at first visit.

Children were prospectively evaluated at four time points: at diagnosis, within 1 month, 6 months and 1 year after diagnosis or at the time of relapse. At diagnosis and at 12 months or at the time of relapse all patients were assessed endoscopically and histologically. Colonoscopic grade of inflammation was determined by use of Matts' colonoscopy grading score (10). Colonoscopy report system required segmental descriptions (rectum, sigmoid, descending, transverse and ascending colon, and caecum). From the information provided on the colonoscopy report, for each segment of the colon was designated a score, and a mean score for that colonoscopy was derived. All histologic specimens were reviewed under code by a single pathologist experienced in analysing paediatric intestinal biopsies, blinded to the patients' clinical details, who scored biopsies according to the Matts' histologic criteria (10).

At baseline, a detailed questionnaire was completed for each subject and control, including details of family, personal history of atopic disease and the presence of allergic symptoms. Family and personal history of atopic disease as well as the presence of allergic symptoms in children were established through the use of the validated ISAAC questionnaire (11). Skin prick tests (SPT) were performed according to a standard technique for common inhalational (*Dermatophagoides pteronyssinus* and *farinae*, *graminacea*, *parietaria* and cat dander) and dietary allergens (whole milk, alpha-lactalbumin, beta-lactoglobulin, casein, albumin, egg yolk and fish) (Lofarma®, Milano, Italy). The tests were carried out on the volar side of the forearm with disposable prick lancettes by one physician who was not aware of the subject's clinical history (MM). Histamine chloride at 10-mg/mL and glycerosaline solution were used as positive and negative controls. After 15 min, weal diameters >3 mm, compared with positive and negative controls were considered positive. Specific IgE levels were considered positive if >0.70 kU/L, as the reported reference ranges for the commercial test used in our laboratory (Unicap-specific IgE allergen immuno cap, manufactured by Pharmacia). Subjects with specific IgE and/or prick tests positive for at least one allergen and a personal history of atopy (such as recurrent symptoms of rhinitis, dermatitis, bronchospasms) were considered atopic children.

Statistical analysis

Data were analysed for all patients who had completed at least two visits. Means and medians were calculated for dimensional variables after controlling for normality of distribution. Statistical analysis was carried out using SPSS statistical software package for Windows (13.0; SPSS Inc., Chicago, IL, USA). The Student's t-test and Mann-Whitney U-test for normally distributed variables and the chi-

squared and Fisher exact tests for categorical variables were used where appropriate. Survival analysis was used to analyse the data set with respect to relapse. The Kaplan–Meier method was used to estimate the survivor function, and comparison of cumulative relapse rates between treatment groups was tested by the log-rank test. The study was approved by the Institutional Review Board of the University of Naples ‘Federico II’. Written, informed consent was obtained from participants’ parents, and assent was obtained for all patients older than 10 years of age.

RESULTS

Thirty-two patients with newly diagnosed UC were screened. Three subjects were excluded, because the parents of two refused consent and one had received previous steroid therapy for the presence of concomitant disease (asthma). Twenty-nine children were eligible and participated to this study and were randomly assigned to receive a CMP elimination diet or to continue a free diet associated with concomitant steroid and/or mesalazine induction and mesalazine maintenance treatment. Demographic data for the study groups are listed in Table 1.

The mean PUCAI performed at diagnosis by the paediatric gastroenterologist of each patients did not show

significant differences between CMP elimination diet and free diet patients ($p = 0.5$; OR 1.25; 95% CI 0.9–1.7) (Table 1).

On the basis of the PGA, the severity of the disease was mild in 14.3% of CMP elimination diet patients vs. 33.3% of free diet patients, moderate in 42.9% of CMP elimination diet subjects vs. 53.3% of free diet subjects and severe in 42.9% of CMP elimination diet children vs. 13.3% of free diet group ($p = 0.3$).

Twenty-five of the 29 enrolled patients responded to the IBD induction therapy with a complete remission (86.2%), 12 belonging to free diet group and 13 to CMP elimination diet group ($p = 0.59$). Three patients had a partial response, whereas 1 patient did not respond to induction therapy. Overall, our data showed that 7 of 13 (53.8%) patients treated with CMP elimination diet and 8 of 15 (53.3%) patients on free diet and IBD therapy relapsed within 1 year of follow-up ($p = 1$; OR = 0.8; CI = 0.2–3.7). Among them, 26.6% (4/15) and 38.4% (5/13) relapsed within the first 6 months ($p = 0.45$). Life-table analysis of the relapses in the 2 groups is showed in Figure 1.

Among the CMP elimination diet group, 6 (42.8%) patients were treated with steroids and mesalazine, while 8 (57.2%) patients received mesalazine alone. Ten (66.6%) patients of the free diet group were treated with steroid

Table 1 Baseline characteristics and at 1 year follow-up or at time of relapse in 29 children with newly diagnosed UC

Characteristics	Cow's milk protein (CMP) elimination diet group	Free diet group	p	CMP elimination diet group	Free diet group	p
	T0			T12 or at Time of Relapse		
Sex (n, %)						
Male	9 (64.3%)	5 (33.3%)	0.1			
Female	5 (35.7%)	10 (66.7%)				
Median Age (months; range)	134.5 (57–196)	138 (55–204)	0.8			
Male	145 (57–196)	157 (81–172)	0.5			
Female	124 (112–173)	133 (55–204)	0.8			
Mean Z-Score (range)	−0.18 (−3 to 2)	0.3 (−1.5 to 2)	0.4	−0.23 (−0.5 to 2.47)	0.6 (−1.1 to 2.2)	0.3
Duration of breast feeding (days, median, range)	97.5 (1–745)	90 (1–262)	0.3			
Introduction of cow's milk (days, median, range)	106 (1–185)	100 (1–170)	0.4			
PUCAI (median, range)	36.2 (15–45)	31 (15–55)	0.5	24 (0–85)	17.5 (0–65)	0.6
Paris classification (n, %)						
Negative (E0)			0.2	3 (21.4)	2 (13.3)	0.2
Proctosigmoiditis (E1)	4 (28.5)	3 (20)		2 (14.3)	2 (13.3)	
Left-sided colitis (E2)	1 (7.1)	2 (13.3)		2 (14.3)	4 (26.6)	
Extensive colitis (E3)	1 (7.1)	5 (33.3)		2 (14.3)	3 (20)	
Pancolitis (E4)	8 (57.1)	5 (33.3)		5 (35.7)	4 (26.6)	
Endoscopic Matt score (mean, range)	1.7	2.2	0.7	2.2	2.5	0.5
Histological Matt score	2.6	2.6	0.8	1.8	2.1	0.4
Steroid therapy	6 (80%)	10 (50%)	0.3			
Time to weaning						
Steroids (days, median, range)	55 (30–60)	60 (30–120)	0.7			
Total amount of Steroid						
Induction Therapy (mean mg/kg)	0.78	0.83	0.3			
Hemoglobin (median, range)	11.7 (5.5–14.1)	11.7 (7–14.3)	0.9	11.5 (7–14.2)	12.1 (9.4–13.7)	0.6
CRP (median, range)	0.3 (0.2–9.1)	0.7 (0.2–19.1)	0.1	0.6 (0.3–86.7)	0.3 (0.3–33.5)	0.6
ESR (median, range)	6.5 (3–25)	13 (3–46)	0.1	12 (1–60)	4 (2–20)	0.3
Calprotectin (median, range)	434.5 (60–500)	369 (15–500)	0.5	144.5 (15–500)	416.5 (53–500)	0.3

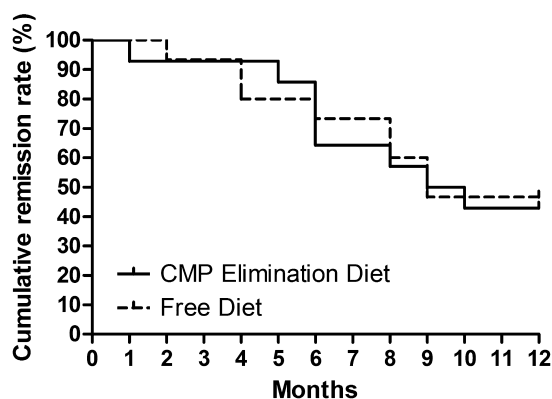


Figure 1 Kaplan-Meier estimates of relapse during treatment on cow's milk protein elimination diet or on free diet (log-rank test $p = 0.87$).

therapy and 5 (33.4%) with mesalazine alone. Overall, the number of relapses was significantly higher in patients treated with steroids and mesalazine versus patients receiving mesalazine alone (12 vs. 3; $p = 0.009$). No other significant differences were observed among the other therapeutic subgroups.

At time of enrolment, endoscopic and histological scores were not statistically different comparing the CMP elimination diet and free diet groups ($p = 0.7$ and $p = 0.8$) (Table 1). At baseline, laboratory parameters including haemoglobin, erythrocyte sedimentation rate and C-reactive protein were not significantly different between the two groups and were not predictive of response and/or relapse (Table 1). Hypereosinophilia was present in 2 patients (6.9%), one from the CMP elimination diet group and 1 from free diet group. At 12 months or at time of relapse, endoscopic and histological scores were not significantly different among the CMP elimination diet group and the free diet group. All patients were compliant to the dietary restrictions.

No side effects or significant changes from baseline values in any of the laboratory parameters examined attributable to CMP elimination diet was registered.

All 29 patients completed the questionnaire. Family history of atopy was present in 4 patients on CMP elimination diet (28.6%) and in five patients on free diet (33.3%) ($p = 1$). Based on the criteria listed under the Methods section, the prevalence of atopy in our study population was 27.5%. Four patients on CMP elimination diet (28.6%) and in five patients on free diet (33.3%) also satisfied the diagnostic criteria for atopy ($p = 1$). Positive laboratory results consistent with atopy for these patients are summarized in Table 2. None of the patients had symptoms of cow's milk allergy. On the basis of PUCAI, remission was achieved in four atopic patients (100%) treated with elimination diet and IBD therapy and in four atopic patients (80%) treated with free diet and IBD therapy ($p = 1$). One patient treated with free diet and IBD therapy had just a partial response. Two of four (50%) atopic patients treated with CMP elimination diet and IBD therapy

Table 2 Clinical and laboratory results in UC atopic children who satisfy criteria for atopy

	Cow's milk protein elimination diet group n (%)	Free diet group n (%)
Family history of atopy	4 (28.6)	7 (46.6)
Associated symptoms	3 (21.4)	2 (13.3)
RAST	1 (7.1)	4 (26.6)
β Lactoglobulin	1 (7.1)	3 (20)
Dermatophagoides pteronyssinus	1 (7.1)	2 (13.3)
Grass pollens	1 (7.1)	0
Cat dander	1 (7.1)	0
Parietaria	0	1 (6.6)
PRICK	2 (14.3)	4 (26.6)
Dermatophagoides pteronyssinus	0	1 (6.6)
Parietaria	1 (7.1)	3 (20)
Grass pollens	2 (14.3)	1 (6.6)
Egg white	1 (7.1)	1 (6.6)
Cat dander	0	0
Casein	0	0
β Lactoglobulin	0	1 (6.6)

and one of five (20%) atopic patients on free diet relapsed within 1 year of follow-up ($p = 0.5$).

DISCUSSION

In this study, we did not demonstrate a significant efficacy of CMP elimination diet in the induction and maintenance of remission in paediatric active UC. Patients receiving CMP elimination diet and concomitant conventional therapy did not have a significantly higher rate of remission compared to children on free diet with not significantly lower incidence of relapse within 1 year of follow-up.

The aetiology of IBD is considered multifactorial. Genetic, infective and environmental theories exist, as well as those centred around host immunity, intraluminal gut flora, food allergies and hypersensitivity (12). Diet may influence gut inflammation through several biologically plausible mechanisms, including antigen presentation, change in prostaglandin balance, and alteration of the microflora (13). The belief that dairy products can exacerbate the disease and that patients restrict their consumption has already been documented (14). From a historical perspective, the concept of 'milk allergy' was introduced in the early part of this century when it was believed that foods and eating habits were involved in the pathogenesis of IBD (15,16). The concept of 'milk allergy' as initially proposed was not based on objective immunologic testing and gradually gave way to theories involving malabsorption of and 'intolerance' to lactose in the 1960s (17) and, more recently, intolerance to other components of dairy products (18). Allergy to milk proteins still remains a possible cause of 'dairy sensitivity' or milk intolerance in a small percentage of IBD patients (19). Even if, so far, the only

recognized evidence is that the lack of breast feeding and an increased prevalence of cow milk sensitivity may be risk factors for the later development of IBD, clinicians still focus on the foods that patients associate with their symptoms and therefore avoid (20,21). However, several reports have demonstrated that inadequate caloric intake is the primary cause of growth retardation in IBD (22,23). All clinicians should be aware that iatrogenic dietary restrictions, which are often imposed without a sound scientific or clinical basis, further reduce the amount of calories provided, contributing to the malnutrition and various micronutrient deficiencies in paediatric IBD patients (24).

Analysing the different therapeutic subgroups (steroids and mesalazine vs. mesalazine alone) within 1 year of follow-up, we found a higher incidence of relapses in patients under steroid therapy of both CMP and free diet groups compared with patients treated with mesalazine alone. This finding clearly highlights that neither steroids nor CMP elimination diet were able to modify the natural history of the disease. Patients eligible for steroid treatment, and therefore with the worst onset of disease, continue to act with the same severe phenotype despite a more aggressive therapy.

The prevalence of atopy in our study population was 27.5%. Our results showed no difference in the prevalence of atopy among UC children treated with elimination diet and those on free diet. Nevertheless, due to the small number of our patients, we cannot draw any conclusion in respect of the association between atopy and UC. Several studies tried to investigate the attractive hypothesis that IBD may be an allergic response to food (21,25) especially in individuals susceptible to various allergens. In particular, UC with Th2 cytokines pattern response has always been thought to be somehow related to allergic diseases. Most studies confirmed the observation that atopic features are more frequent in patients with IBD than in the general population (26,27). Only one study by Troncone et al. (28) showed that there was no correlation between atopy and IBD.

Our study has some limitations. First of all, we did not evaluate our children for lactase deficiency or lactose intolerance. Lactase deficiency is common in adults with chronic IBD (29). Complete avoidance of milk and milk products can obviate the symptoms of lactose malabsorption, although decreasing the milk intake may also prevent discomfort. As many as 80% of gastroenterologists surveyed indicated that they have recommended avoidance of milk and milk products to patients with UC (29). It has been reported that more than one-third of paediatric patients with IBD have lactase deficiency. Nevertheless, avoidance of a lactose-containing diet should not be routinely recommended to paediatric patients with IBD until evaluation for lactase deficiency or lactose intolerance is performed (30).

Another limitation of our study is the small number of patients. Because we had negative results (i.e., we did not find a statistical difference), and the sample size of the cohorts is somewhat small, it is likely that the lack of significant difference occurred by chance. However, because there are no trends towards significance, we doubt

that there is the risk of a type II statistical error in our study. Therefore, we believe that CMP elimination diet does not appear to be useful in the therapy of UC of children.

In conclusion, data of this paediatric, randomized trial suggest that CMP elimination has no role in the management of UC in non-sensitized children. Further larger studies are needed to evaluate the efficacy of the CMP exclusion diet on the induction and maintenance of remission in UC atopic children.

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