Polymeric Diet Alone versus Corticosteroids in the Treatment of Active Pediatric Crohn’s Disease


Rating: Of importance.

Introduction: Nutritional therapy has been reported to have an almost equivalent efficacy to that of corticosteroids in achieving clinical remission in active Crohn’s disease (CD). However, the effects of both treatments on intestinal mucosal inflammation rarely are reported. In a randomized controlled trial in children with active CD, the authors compared the efficacy of nutritional therapy alone with that of corticosteroids on clinical variables and intestinal mucosal healing.

Methods: In a prospective, 10-week, open-label trial, children with active, naïve CD were randomly assigned to oral polymeric formula alone or oral corticosteroids. The clinical activity index and nutritional and activity serum variables were evaluated at week 0 and subsequently every 2 weeks; intestinal mucosal inflammation was assessed through endoscopy and histology at weeks 0 and 10. Primary efficacy outcomes were clinical remission and mucosal healing.

Results: Of the 37 children randomized, 19 received polymeric formula and 18 received corticosteroids. At week 10, on an intention-to-treat basis, the proportion of patients achieving clinical remission was comparable between the two groups (polymeric formula: 15/19 [79%; 95% CI, 56%–92%]; corticosteroid group: 12/18 [67%; 95% CI, 44%–84%]; P=0.4; not significant). In contrast, the proportion of children showing mucosal healing was significantly higher in the polymeric (14/19; 74%; 95% CI, 51%–89%) than the corticosteroid group (6/18 [33%; 95% CI, 16%–57%]; P<0.05). At week 10, both endoscopic and histologic scores significantly decreased only in the polymeric group (P<0.001).

Conclusions: In children with active and recently diagnosed CD, a short course of polymeric diet is more effective than corticosteroids in inducing healing of gut inflammatory lesions.

Editor’s comments
Crohn’s disease is a lifelong inflammatory bowel disease with a peak of onset during adolescence. It afflicts half a million individuals in North America [1]. Primary drugs used to induce remission of disease activity have been corticosteroids and aminosalicylates. Other agents have generally been used for their steroid-sparing effects or for refractory patients: thiopurines, methotrexate, cyclosporine, and infliximab [2]. For more than two decades, however, nutritional therapy has been examined as an alternative to medication for induction of remission [3–6].

Previous comparisons between nutritional therapy and corticosteroids, as summarized in a meta-analysis [4], have used clinical status as the primary outcome measure, finding corticosteroids to be equal to, or perhaps slightly superior to, nutritional therapy. The current study differs from these previous clinical trials in that it includes endoscopic and histologic outcome measures, the only measures in this trial that clearly respond better to nutritional therapy than to corticosteroids.

This clinical trial, by a superb group of clinical researchers, manifests many strengths. It is prospective and includes a detailed prospective power analysis. Children were assigned randomly between the two treatments. Although blinding of the randomization was not feasible, masking of the allocation and the clinical response was accomplished for the endoscopist and the pathologist who scored the primary outcome measures: the endoscopic and histologic scoring. These outcome measures, quantified without knowledge of treatment allocation, were also the ones achieving significance.

Another strength, often absent from clinical trials in children, was the use of previously validated and published outcome measures: the Pediatric Crohn’s Disease Activity Index (PCDAI) for the clinical outcome; the Crohn’s Disease Endoscopic Index of Severity for the endoscopic outcome; and a scoring system for acute and chronic changes of ileal and colonic histology for the histologic outcome.

A clinical trial for a complex, multifaceted disease is a challenge on many fronts. Prospectively defined exclusion criteria must eliminate children for whom the therapies might not be ideally safe or efficacious yet not exclude so many forms of the disease that the results are irrelevant to most of the diseased population presenting for treatment. The authors of this clinical trial seem to have done...
an excellent job in meeting these objectives. Recruiting children with moderate or severe CD diagnosed within 3 months before enrollment, they excluded those with fistulizing, stenosing, or anorectal CD as well as those with systemic or other system disease or with contraindications to either therapy. These exclusions only affected three of 41 children assessed for eligibility, with a fourth child refusing consent. A clear flow chart tracks the children, ages 4 to 17 years, through the two arms of the study, showing that, of the 37 randomized to either treatment, two in each group failed to reach the 10-week outcome assessment point. The two in the nutritional arm failed because of inability to introduce the formula, and the two in the steroid arm failed because of worsening of disease activity. One further child (in the steroid arm) refused the follow-up endoscopy, but the treatment of the data for that child is a bit unclear to this reader.

Previous treatment may affect the results of the study, and in this respect the study is not so “clean,” although previous treatments are distributed fairly evenly between the two treatment groups. The protocol excluded any child who had received prior treatment with azathioprine/6-mercaptopurine, cyclosporine, or other immunosuppressive drugs. It prohibited corticosteroids within 4 weeks before randomization. It allowed sulfasalazine or mesalazine if the dosage had been stable for at least 4 weeks and if the drug had been discontinued at least 5 days before the randomization visit. The results of recruitment were that the patients randomized to the polymeric diet had taken sulfasalazine (14/19, 74%), mesalazine (10/19, 53%), and steroid (6/19, 31%), whereas for those randomized to corticosteroids the numbers were sulfasalazine (15/18, 83%), mesalazine (8/18, 44%), and steroid (7/18, 38%). In a study of limited size, inclusion of such patients may have led to bias: Were those patients who enrolled ones who had not responded to their prior therapy? In that case, 38% of those randomized to corticosteroids could have failed to respond to as much as 8 weeks of prior therapy with steroids, perhaps selecting a group predestined to fail with that particular therapy. In contrast, apparently none of the subjects had had (or had failed) previous trials of nutritional therapy. Other potential biases could be the specific form of each of the treatments and the choice of the “dose” employed.

For the nutritional therapy, the investigators used Modulen (Nestle Nutrition, Glendale, CA), a polymeric formula made up of casein (14% of calories), glucose polymer/sucrose (44%), and milk fat/corn oil/medium-chain triglycerides (42%). Modulen also includes transforming growth factor β; 4% or less of calories as n-6 polyunsaturated fatty acids; and adequate vitamins, minerals, and trace elements. Its osmolality is 370 mosm/L, and its caloric density is 1 cal/mL. It was “dosed” at 120% to 130% of the recommended daily requirement for each patient and given by nasogastric tube if it could not be consumed orally.

For the corticosteroid, oral methylprednisolone was used, dosed at 1.6 mg/kg/d (up to maximum 60 mg) for 4 weeks, then tapered by 5 mg (if starting dose was <40 mg) to 10 mg (if starting dose was >40 mg) each week over 6 weeks, to 5 to 10 mg/kg. Disease flares during taper were managed by a return to the previously effective dose for 2 to 4 weeks. The duration of administration of the induction dose before tapering was shorter than what some studies have employed and might be responsible for the failure of endoscopic/histologic remission in steroid-treated patients at 10 weeks after start of induction. Alternative strategies that were not tested during this study were a longer period of induction dosing, a slower taper, a longer period before endoscopic examination, or the use of alternate day dosing at a higher level (eg, 30 mg every other day) as the endpoint before endoscopy [7]. One could hypothesize that each of these alternative strategies might have improved the efficacy measures for the corticosteroid group, although they might also have produced a higher rate of side effects.

The effectiveness of nutritional therapy for CD has been documented in a multitude of reports. A perplexing question about this therapy is why it should work at all. Although patients who are newly symptomatic with inflammatory bowel disease may be anorectic and have symptoms when they eat, they are not fasting. Initially, when elemental diets were the principal ones evaluated for efficacy, it was proposed that reduction of antigen load was responsible. Subsequently, as in the current study, polymeric diets have shown similar effectiveness, providing an argument against a role for antigenicity. Other proposed mechanisms, as discussed by the authors, include provision of essential nutrients or other factors, such as transforming growth factor β2; decreasing fat content or improving fat composition; altering intestinal microflora; improving immunologic function; or providing anti-inflammatory effects.

An obvious question, for a study that finds a failure of histologic improvement in clinically improved children only in the group randomized to corticosteroid, is, “so what?” If a difference makes no difference to the patient, is it important? The authors emphasize that failure of the corticosteroids to improve the endoscopic and histologic lesions may be important by leaving the gut more susceptible to subsequent relapse, and they emphasize this concept with citations from existing literature. This view considers the endoscopic and histologic healing to represent a more fundamental improvement in the disease than that evidenced solely by clinical remission.

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It is my impression that nutritional therapy is used for remission induction in only a minority of centers, at least in
the United States. Why do clinicians treating children with inflammatory bowel disease not use nutritional therapy more aggressively, given the preponderance of evidence of its effectiveness, combined with the relative lack of side effects? The institution of nutritional therapy, at least as conducted in the current study, was done during a several-day hospitalization, with consultation services of a dietician. Nearly a quarter of the children assigned nutritional therapy required overnight nasogastric intubation for infusion of the prescribed caloric “dose,” making the therapy logistically more complex than the simple prescription of tablet dosing of methylprednisolone. Such a regimen may meet more resistance from the children and their parents initially. Even with the intensive support inherent in a clinical trial, more than 10% of the children assigned nutritional therapy failed to accomplish introduction of the formula.

In conclusion, this well-done and nicely reported study adds to the accumulating information supporting use of nutritional therapy for remission induction in children with Crohn’s disease. It will be useful to have a clearer understanding of the mechanisms of the effectiveness of this therapy, as well as improved methods of administering the crucial aspects of it noninvasively, in order to improve its acceptability to children, their parents, and their physicians.

References