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Clinical Trials Study

Effect of oral polymeric, TGF-beta 2 enriched diet (Modulen) *vs* Budesonide on clinical response and mucosal healing in Crohn's patients

Modulen *vs* Budesonide in Crohn's disease

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Abstract

BACKGROUND

Mucosal healing has become an important goal of Crohn's disease (CD) treatments. Modulen, enriched with TGF-beta 2, and Budesonide are commonly accepted treatments for mild-moderate CD. However, their effects on the small bowel (SB) mucosa remain underexplored.

AIM

To prospectively assess clinical and mucosal responses to Modulen vs. Budesonide in adults with CD, using small bowel capsule endoscopy.

METHODS

Thirty patients were divided into two groups: Modulen+ home-based diet (21 patients) and Budesonide (9 patients) for an eight-week intervention followed by four weeks of follow-up. Clinical, laboratory, and endoscopic responses were evaluated. The mucosal changes were assessed through SB capsule endoscopy.

RESULTS

Results indicated significant clinical improvement in the Modulen group with reduced Crohn's Disease Activity Index (CDAI) (P = 0.041) and improved Inflammatory Bowel Disease Questionnaire (IBDQ) score (P = 0.016). Moreover, Modulen was associated with a significant small bowel mucosal improvement, evidenced by a decrease in Lewis score (P = 0.027). No significant changes were observed in calprotectin or other laboratory parameters. Conversely, Budesonide exhibited more modest clinical effects, but it improved calprotectin, hemoglobin, and C-reactive protein (CRP) levels (P = 0.051, P = 0.014, and 0.038, respectively). The capsule endoscopy did not reveal a significant mucosal response in the Budesonide group.

CONCLUSION

Both interventions have a role in CD treatment. Yet, their effects differ and may complement each other: Modulen yields clinical and mucosal improvements, while Budesonide primarily leads mainly to laboratory improvements.

Key Words: Crohn's disease; Modulen oral polymeric diet; TGF-beta 2; Budesonide; Mucosal healing; Clinical response; Capsule endoscopy; Small bowel capsule.

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Core Tip: The effects of Modulen and Budesonide on mucosal healing in Crohn's disease remain underexplored. In this study, the small bowel capsule endoscopy was used for the first time to compare the mucosal effect of Modulen and Budesonide on patients with newly diagnosed mild-moderate Crohn's disease. The study results demonstrate that Modulen shows significant clinical and mucosal improvements, while Budesonide primarily improves laboratory parameters. The complementary effect of both of them should be explored to maximize the benefit to the patients.

INTRODUCTION

In recent years, the management goals for Crohn's disease (CD) have shifted from treating only symptoms to striding to achieve mucosal healing[1-3]. Mucosal healing has been shown to reduce long-term complications and improve patient outcomes[1-3]. Mucosal healing can be evaluated using colonoscopy in the colon and capsule endoscopy/ computed tomographic enterography (CTE) / magnetic resonance enterography (MRE) in the small bowel (SB). SB capsule endoscopy is considered to be the most sensitive tool for assessing SB mucosal disease[4-9], and several studies demonstrated its superiority over CTE/MRE[10-12].

Modulen IBD is a polymeric, nutritionally complete oral formulation enriched with transforming growth factor-beta (TGFβ2). Traditionally, Modulen has been used for both active-phase treatment and maintenance of Crohn's disease. Modulen's potential mechanisms of action in CD include a direct anti-inflammatory effect of TGFβ2, which decreases mucosal inflammation by modulating mucosal T-helper 1 cells, and a prebiotic effect that supports the growth of beneficial gut bacteria[13-16]. Budesonide is a locally acting corticosteroid and a well-accepted treatment for CD. Even though both Modulen and Budesonide are standard and popular treatments for mild-moderate CD, the effect of either of these treatments on the mucosal healing of the small bowel has not been adequately explored. Specifically, no prior study has comprehensively examined the mucosal effects of Modulen or Budesonide throughout the entire SB using capsule endoscopy.

This prospective pilot study aimed to evaluate the clinical response and mucosal healing effects (using SB capsule) of an oral polymeric diet enriched with TGF-beta 2 (Modulen) compared to Budesonide in adult patients newly diagnosed with Crohn's disease.

MATERIALS AND METHODS

Study design: This prospective, open-label, pilot randomized study was conducted at the Department of Gastroenterology in Hillel Yaffe Medical Center, Israel, from May 2020 to May 2023. A Helsinki committee of Hillel Yaffe Medical Center approved the study protocol (IRB—HYMC 0128-18). The study was registered on https://clinicaltrials.gov/ under the number NCT04233463. All patients provided informed written consent prior to study enrollment.

Study population: The study included newly diagnosed Crohn's patients with mild to moderate disease and SB or SB-colon involvement.

The inclusion criteria:

Patients aged 18-70 with newly diagnosed mild-moderate CD (Crohn's Disease Activity Index (CDAI) 150-450) or Lewis score > 135 (within three months since diagnosis), who had not yet started any medical treatment

Crohn's patients with small bowel or combined SB and colonic disease.

Recent completion of SB capsule and colonoscopy (within three months before the enrolment)

The exclusion criteria:

Previous bowel surgery (cholecystectomy or appendectomy was not an exclusion criteria)

Obstructive symptoms or radiologic evidence of significant intestinal stricture

Commonly accepted contra-indications for capsule endoscopy (pacemaker, swallowing problems, etc).

Ileoscopy, colostomy

Pregnancy, lactation

Commonly accepted contra-indication for steroid treatment (uncontrolled diabetes mellitus, hypertension, *etc*.)

Group selection: Patients were divided into two groups based mainly on patient preference.

Intervention:

Nutritional treatment (Modulen group): Patients received Modulen at a dosage of 4 portions (over-all 1000 mL with a content of 1000 kcal) combined with a homemade diet without calorie restrictions. Modulen IBD (Nestle, Vevey, Switzerland) is a polymeric diet with casein as its protein source and is rich in TGFβ2. The homemade diet is a diet based on home-cooked food and excludes processed or fast food, emulsifiers. It contains very limited amounts of lactose, spices, and preservatives.

Medical treatment (Budesonide group): Patients received Budesonide 9 mg in three divided doses daily without any dietary modifications. Budesonide is a locally acting steroid released in the ileum of the small intestine and the right colon. It has a high first

bypass metabolism in the liver which minimizes its systemic side effects. The patients were instructed to continue the same nutritional habits as they had before the study.

Duration: The intervention period lasted eight weeks, followed by a four-week follow-up period.

Criteria for the withdrawal:

Intolerance to nutritional treatment

Adverse effects of Budesonide or Modulen

CD exacerbation during treatment (increase of > 70 points in CDAI compared to baseline)

Patient's non-compliance

Patient withdrawal of consent

Outcome Measures:

Clinical and laboratory assessments, including medical history, physical examination, blood and stool tests, patient symptom questionnaire, CDAI score, and Inflammatory Bowel Disease Questionnaire (IBDQ), were conducted at baseline, monthly during intervention, post-intervention, and after one month of follow-up. Compliance was assessed. Participants maintained food diaries (3-day food intake records) before and during the intervention. A Total Symptoms Score was derived from the patient symptom questionnaire, comprising abdominal pain, bloating, gas symptoms scored from 0-10, and daily bowel movements. The score average of these four parameters provided us with a Total symptoms score.

Mucosal inflammation was assessed in the small bowel and colon using small bowel capsule endoscopy (Lewis score) and colonoscopy (Simple Endoscopic Score for Crohn's disease (SES-CD)). Small bowel capsule endoscopy was performed before and immediately after the eight-week intervention, using Capsule endoscopy equipment of Medtronic, Minneapolis, Minnesota, USA (PillCam SB3 capsules, Rapid 9 Software, DR3, and sensor belts). A gastroenterologist with expertise in capsule endoscopy

performed the interpretation of capsule study results and Lewis scoring. The Lewis score integrates the degree of inflammation in the most inflamed small bowel tertile and stenosis, providing a comprehensive assessment of mucosal changes. Separate Inflammatory score (a sum of inflammatory scores in three tertiles) and Stenosis scores were calculated to offer additional insights into small bowel mucosal changes.

Colonoscopy, including ileoscopy, was performed before intervention. If colonic disease was detected during the initial colonoscopy, a follow-up colonoscopy was conducted immediately after the eight-week intervention. Patients without colonic involvement at the initial colonoscopy were spared from the second procedure.

Statistical analysis:

Descriptive statistics were used for continuous variables, including mean, standard deviation, median, and percentiles, while categorical variables were analyzed using frequency distributions. The Kolmogorov-Smirnov test assessed normal distribution, with subsequent Mann-Whitney *U* test or t-test applied for group comparisons. Friedman and ANOVA tests were employed to detect differences across three assessment time points (baseline, after one month, and after two months). Intention-to-treat and per-protocol analyses were conducted. Statistical significance was defined at a confidence interval of 95% ($P < 0.05$).

Comparisons between groups regarding demographics, Lewis scores (Total and Inflammatory), SES-CD score, and IBDQ score were performed using Chi-square, Fisher's Exact, unpaired t-tests, and Mann-Whitney tests, if applicable. One-way ANOVA and Kruskal-Wallis tests assessed continuous variable differences between groups. Post hoc tests using Mann-Whitney tests with Bonferroni adjustment were performed when appropriate. Spearman's correlation coefficient calculations assessed correlations between clinical and endoscopic parameters. SAS for Windows 9.2 was used for all statistical analyses.

Clinical response in each group was defined as a statistically significant decrease in CDAI, Total Symptoms Score, calprotectin levels, C-reactive protein (CRP) levels, and a

significant increase in IBDQ at the end of intervention compared to baseline. Endoscopic response was defined as a statistically significant decrease in Lewis score or its parameters (Inflammation and Stenosis scores) and SES-CD score.

RESULTS

Thirty patients participated in the study (21 in the Modulen+Home-based diet group, 9 in the Budesonide group). Baseline demographic, clinical, and endoscopic parameters were similar between groups, with no significant differences in age, BMI, gender distribution, and time since CD diagnosis (Table 1). None of the patients had previous bowel surgery or previous medical or nutritional treatment. Most patients in both groups had exclusive small bowel involvement (> 80% of patients). Baseline assessments indicated comparable CD severity, as evidenced by CDAI, IBDQ, Total Lewis score, Inflammatory score, SES-CD, Total Symptoms Score, CRP, albumin, and hemoglobin. Only the calprotectin level showed a borderline difference between the groups (Modulen group: 59 µg/mg, Budesonide group: 336 µg/mg, $P = 0.055$). A small number of patients in both groups had colonic involvement (overall, five patients in both groups); when present, it was mild.

Randomization was performed based mainly on patients' preferences. Despite the preference of many patients for nutritional treatment (21 patients), a higher withdrawal rate was observed in the Modulen group (52.3%) compared to the Budesonide group (22.2%). As a result, only 11 patients in the Modulen group and seven in the Budesonide group completed the eight-week treatment. Reasons for withdrawal in the Modulen group were primarily related to Modulen itself (taste, cost, gastrointestinal (GI) symptoms; 7 patients), withdrawn consent (3 patients), and loss of follow-up (1 patient). Among patients who completed the entire intervention, Modulen compliance was satisfactory (3 portions during the first four weeks and 2.8 portions during the last four weeks), and no significant adverse effects were recorded during Budesonide treatment. Two patients in the Budesonide group did not complete the study (1 patient withdrew consent, and one patient experienced disease exacerbation).

All patients in both study arms underwent the SB capsule study twice (before and after the intervention), except one patient who had a capsule study only at the enrollment. All capsule studies were technically successful except for one incomplete study. No instances of capsule retention were found.

Colonoscopy was performed before the intervention in all patients and revealed no colonic inflammation in most of the patients or a minimal inflammation in the rest of them. Therefore the second colonoscopy at the end of the intervention was no needed.

Outcome Measures:

Intention-to-Treat Analysis for Modulen Group (n = 21) (Table 2): Clinical disease activity significantly decreased, as reflected by CDAI, IBDQ, and Total Symptoms Score after four and eight weeks of treatment. During the follow-up period, some increase in disease activity was observed, but all P values remained significantly lower compared to baseline. Endoscopic activity, measured by the Total Inflammatory Score (the sum of inflammatory scores of three small bowel tertiles), indicated a significant reduction after eight weeks of intervention (P = 0.0035). However, the Lewis score, representing both inflammatory and stenosis scores, showed some decrease but did not reach statistical significance. No significant laboratory improvements were observed due to nutritional treatment.

Per-Protocol Analysis for Modulen Group (n = 11) (Table 3): Per-protocol analysis of 11 patients who completed eight weeks of nutritional treatment confirmed significant improvements in CDAI, IBDQ, and a near-significant improvement in Total Symptoms Score. Moreover, improvements were observed in the Lewis and Total Inflammatory scores, mainly driven by mucosal improvement in the middle small bowel segment. A near-significant reduction in calprotectin levels was recorded after the first four weeks (P = 0.051).

Intention-to-Treat and Per-Protocol Analyses for Budesonide Group (n = 9, n = 7) (Tables 4,5): The clinical and endoscopic response to Budesonide was more modest. CDAI temporarily improved during the first four weeks of treatment but lost

significance during the last four weeks and the follow-up period. Other clinical parameters and all endoscopic capsule parameters showed no significant improvement. However, per-protocol analysis in the Budesonide group demonstrated significant improvements in calprotectin, hemoglobin, and CRP levels.

DISCUSSION

This pilot study provides valuable insights into the effects of Modulen and Budesonide on clinical response and mucosal healing in adult patients with newly diagnosed Crohn's disease. Modulen, combined with a home-based diet, demonstrated positive impacts on both clinical response and mucosal healing in the small bowel. In contrast, Budesonide treatment did not lead to sustained clinical response or mucosal healing but did significantly improve laboratory parameters such as calprotectin, hemoglobin, and CRP levels. The results suggest that both interventions play a role in Crohn's disease treatment, with differing and sometimes complementary effects.

Modulen is a nutritional formula enriched with TGFβ, which undergoes digestion and absorption in the proximal and middle SB. Therefore, a mucosal improvement, especially in the middle SB tertile, as demonstrated by the capsule in this study, has a rational explanation. On the contrary, Budesonide, a locally acting steroid, is released from granules in the distal ileum of the small intestine and the right colon. Some could expect a mucosal improvement in the distal/terminal ileum, but no such effect was demonstrated in our study.

While Modulen has been studied in children and adults in various clinical contexts, none of these studies comprehensively assessed its impact on mucosal healing.

Most of the studies conducted in the pediatric population did not evaluate a mucosal healing response[17-25], except for one[26], that assessed a colonic mucosal response whereas Modulen's primarily effects SB[26]. As for now, there are only five published studies on Modulen's effect in Crohn's disease adult patients. A pilot study in adults suggested that Modulen, in addition to standard therapy, may help to induce remission in the active phase of Crohn's disease[27]. Another study addressed maintenance of

remission in adults, comparing the efficacy of Modulen to mesalamine, and suggests no difference in either arm[28]. The third study in adults evaluated the ability of preoperative ANS-TGF-β2 to decrease postoperative complications after surgery for complicated ileocolonic disease[29]. The results were favorable to Modulen treatment. In none of these three studies, a possible effect of Modulen on SB mucosal healing was evaluated. The studies of Ferreira and Yanai *et al*.[30,31] included endoscopic evaluation but were limited to colonoscopy with ileoscopy only. In addition, the primary aim of the Yanai *et al*. study[31] was the effect of the CDED diet. At the same time, Modulen was a part of complex nutritional intervention only and was not evaluated separately[31].

Similarly, studies on Budesonide are limited[32-35], with only one previous study evaluating its mucosal effect by ileocolonoscopy[36]. In this randomized controlled trial, Mantzar and coauthors[36] compared the efficacy of azathioprine (2.0–2.5 mg/kg daily) *vs* Budesonide (6–9 mg daily) in patients with steroid-dependent Crohn's ileocolitis or proximal colitis who were in clinical remission; this study evaluated mucosal healing at one year using the CDEIS. Eighty-three percent of the azathioprine-treated patients achieved complete or near complete mucosal healing, compared to only 24% of patients treated with Budesonide (P = 0.001).

None of the previously mentioned studies in pediatric or adult population have used a SB capsule endoscopy to evaluate the effect of Modulen or Budesonide on mucosal healing, despite the fact that the capsule endoscopy is widely used for follow up after the mucosal response of different treatment for about two decades [4-9]. Most of the studies evaluated clinical response only [19-23]. Some of them have integrated ileo-colonoscopy into the methods of endoscopic evaluation. Our study was the first one, which provided a full SB evaluation by capsule endoscopy under Modulen or Budesonide treatments.

An interesting observation was that despite the preference of most patients for nutritional treatment, a higher withdrawal rate was observed in the Modulen group compared to the Budesonide group. As physicians, we should take this observation into

account planning the treatment plan for our patients: Many patients quickly become enthusiastic about the option of different nutritional treatments, but in many cases this enthusiasm quickly fades. On the other hand, the patients hesitate a lot before the drug treatments but when they start the treatment, there is a higher chance that they will stick with it.

Our study has several limitations. The most significant one is a small sample size, especially of Budesonide group. The second limitation is relatively short period of treatment (two months), followed by a follow-up of one months.

CONCLUSION

In summary, our pilot study provides a unique contribution to the field by offering a comprehensive assessment of clinical, laboratory, and endoscopic response to nutritional (Modulen combined with home-base diet) *vs* Budesonide treatment in adult patients with newly diagnosed mild-moderate Crohn's disease. For the first time, SB capsule endoscopy was used for full SB evaluation for endoscopic response to Modulen and Budesonide separately. Future large-scale research could validate our results and explore a third group receiving a combination treatment of Modulen and Budesonide, providing additional insights into their potential synergistic effects.

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