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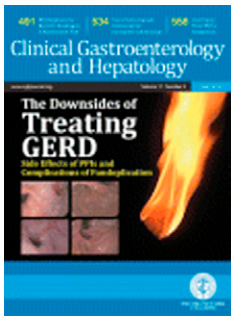

Cannabis Induces a Clinical Response in Patients with Crohn's Disease: a Prospective Placebo-Controlled Study

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Cannabis Induces a Clinical Response in Patients with Crohn's Disease: a Prospective Placebo-Controlled Study

Short title: cannabis for treatment of Crohn's disease

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List of abbreviations:

Crohn's Disease Activity Index (CDAI) tetrahydrocannabinol (THC) cannabidiol (CBD)

Abstract

Background & Aims: The marijuana plant *Cannabis sativa* has been reported to produce beneficial effects for patients with inflammatory bowel diseases, but these have not been investigated in controlled trials. We performed a prospective trial to determine whether cannabis can induce remission in patients with Crohn's disease.

Methods: We studied 21 patients (mean age 40±14 years, 13 male) with Crohn's Disease and activity index (CDAI) scores >200 who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor-α agents. Patients were randomly assigned to groups given cannabis, twice daily, in the form of cigarettes containing 11.5 mg of tetrahydrocannabinol (THC) or placebo containing cannabis flowers from which the THC had been extracted. Disease activity and laboratory tests were assessed during 8 weeks of treatment and 2 weeks thereafter.

Results: Complete remission (a CDAI score <150) was achieved by 5/11 subjects in the cannabis group (45%) and 1/10 in the placebo group (10%; *P*=.43). A clinical response (a decrease in CDAI score of >100) was observed in 10/11 subjects in the cannabis group (90%; from 330±105 to 152±109) and 4/10 in the placebo group (40%; from 373±94 to 306±143; *P*=.028). Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects.

Conclusion: Although the primary endpoint of the study (induction of remission) was not achieved, a short course (8 week) of THC-rich cannabis produced significant clinical, steroid-free benefits to 11 patients with active CD, compared to placebo, without side effects. Further studies, with larger patient groups and a non-smoking mode of intake, are warranted. ClinicalTrials.gov NCT01040910

KEY WORDS: inflammatory bowel disease; Crohn's disease; cannabinoids; endocannabinoid; inflammation

Background

Apart from its recreational properties, the marijuana plant cannabis has been used for centuries as a medicinal treatment for a variety of ailments. The cannabis plant contains over 60 different compounds, collectively referred to as cannabinoids [1]. Although Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) seem to be most active, other yet unknown ingredients may also have beneficial effects. Cannabinoids have a profound anti-inflammatory effect, mainly through the CB2 receptor, while cell mediated immunity was found to be decreased in chronic marijuana users [2]. A potent anti-inflammatory effect of cannabis was observed in rats [3]. Almost all major immune modulation events involve the endocannabinoid system. Cannabinoids shift the balance of pro-inflammatory cytokines and anti-inflammatory cytokines towards a T-helper cell type 2 profile (Th2 phenotype), and suppress cell-mediated immunity, whereas humoral immunity may be enhanced [4]. Cannabinoid exposure antagonizes release of prostaglandins, histamine and the matrix-active proteases from mast cells [5]. The phagocytic function of macrophages is suppressed by cannabinoid exposure. Cannabinoids also suppress inflammation at a secondary, chronic level by down-regulating the production of cytokines such as TNF-α, interferon-γ, and interleukin-1 [6]. They may, therefore, be beneficial in inflammatory conditions.

Within gastroenterology, cannabis has been used to treat anorexia, emesis, abdominal pain, gastroenteritis, diarrhea, intestinal inflammation and diabetic gastroparesis [7]. Cannabinoids were found to ameliorate inflammation in a mouse model of colitis [8]. In 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, cannabinoids decreased macroscopic inflammation, myeloperoxidase activity and peristalsis [9]. The combination of THC and CBD was more effective than either substance alone [10].

In a retrospective, observational study, we recently reported that cannabis had beneficial effects in Crohn's disease [11]. However, to date no placebo controlled trials have been published on the use of

cannabis in inflammatory bowel disease (IBD). We conducted a double-blind, placebo-controlled study to investigate the effects of cannabis on patients with active Crohn's disease.

Materials and methods

The primary objective of the study was the induction of remission, defined as a CDAI score of 150 or less after 8 weeks of cannabis treatment. Secondary objectives were response rate, determined as a 100 point reduction of CDAI, reduction of at least 0.5 mg in CRP or improvement in quality of life of at least 50 points, as measured by the Short form health survey (SF-36).

Patients with an established diagnosis of Crohn's disease, who were referred to the Gastroenterology Institute at Meir Medical Center, a tertiary-care facility, between September 2010 and September 2011 were screened for eligibility. Eligible patients were at least 20 years of age and had active Crohn's disease, with a calculated Crohn's Disease Activity Index (CDAI) score between 200 and 450 points. All patients had failed at least one form of medical treatment for the disease, including mesalamine, corticosteroids, thiopurines, methotrexate or anti-TNF-α. Patients receiving corticosteroids were on a stable dose for at least one month and those receiving thiopurines at least 3 months. Anti-TNF-α failure was declared after at least 4 doses. Patients with short bowel syndrome, symptomatic stricture, abscess, abdominal surgery within the previous 3 months, pregnancy or intention to become pregnant within 6 months, a history of mental illness, drug abuse or previous cannabis consumption were excluded. Patients were also excluded if in their physician's judgment, they might be vulnerable to drug addiction or mental instability. The study protocol was approved by the institutional Ethics Committee. All patients gave written informed consent prior to enrollment. All co-authors had access to the study data and reviewed and approved the final manuscript.

Using the block method [12] in a 1:1 ratio, patients were randomly assigned to receive either medical cannabis or placebo in the form of cigarettes. Both patients and investigators were blinded to the treatment group assignment. Each cigarette contained 0.5 g of dried cannabis flowers (flowers have a higher THC content than leaves), corresponding to 11.5 mg THC. The active cannabis was made from dried flowers of genetically identical plants of *Cannabis sativa* Var. Indica "Erez" (courtesy of Tikun

Olam Ltd., Tel Aviv, Israel), known to contain 23% THC and <0.5% CBD. The placebo was made of cannabis flowers from which THC had been extracted. Dried flowers of Cannabis were mixed with food grade 95% ethanol to cover and allowed to sit in a clean glass jar for two weeks. The alcohol was then decanted and fresh 95% ethanol added to the jar. This procedure was repeated three times. After this, the flowers were covered with a mixture of spirits comprising the first distillate "head" fraction from a proprietary mixture of organically grown pomegranate (*Punica granatum*) juice, pericarps, leaves and flowers that had been allowed to ferment to completion (~2 weeks) in the presence of 0.025% *Saccharomyces cerevisiae* Var. "18" (Courtesy Rimonest Ltd., Haifa, Israel). After three more days, the spirits were decanted and the flowers allowed to dry in ambient air with ventilation for 72 hours. The final product was tested for cannabinoids and shown to contain <0.4% THC and undetectable amounts of all other cannabinoids including CBD. The process was repeated and shown to be reproducible. All cigarettes were machine made to be identical.

Patients were followed for 8 weeks of treatment and 2 additional weeks of "washout" period. Concomitant medications remained constant throughout the study except for corticosteroids, which were tapered when possible. Patients were evaluated at weeks 0, 2, 8, and 10 including medical interview, physical examination, assessment of disease activity (CDAI) and blood tests (complete blood count, liver and kidney function, and CRP). Quality of life (SF-36) and side effect questionnaires were completed on weeks 0 and 8. The side-effect questionnaire included questions about changes in ability to concentrate, work, sleep, abdominal pain, appetite, general well being and general satisfaction with the treatment. Relevant symptoms of drug addiction as defined by the DSM- IV [13] included cravings for a larger dose and ability to continue regular activities, such as work and studies. Answers were graded by severity from 1 to 7.

Statistical Analyses

Numerical results are presented as mean ± standard deviation (SD), while categorical results are shown in percentage. The difference in CDAI between the two groups (study vs. control) was examined as follows: The change (delta) in CDAI between the baseline measurement and after 8 weeks of study was

calculated and the mean delta was compared between the two groups using the t-test for independent groups. In addition, the performance of each group, (i.e the change per group) was also examined by applying the t-test for paired groups for the study and control group separately. For categorical measurements, Chi-square and Fisher's exact tests were used to compare the groups at each time point. The delta SF-36 between the baseline measurement and after 8 weeks of study was calculated and the mean delta was compared between the two groups using the t-test for independent groups. In addition, the difference in side effects between the two sub-groups was examined.Since the measurements were ordered, the Mann-Whitney non-parametric test for independent groups was used. All statistical analyses were done using the statistical software package SPSS, ver. 20.

Results

Of fifty-one patients screened, 29 did not meet the inclusion criteria: 15 had a CDAI less then 200, 7 did not consent, 1 was diagnosed with ulcerative colitis, 3 were designated for surgery (1 due to stricture of the small bowel and 2 due to an intra-abdominal abscess) and 3 were already receiving medical cannabis. Twenty-two eligible patients were recruited. One patient withdrew consent before consumption of the study drug and another after two weeks of treatment. The second patient was included in the analysis. Thus, twenty-one patients, 11 in the study group and 10 in the placebo group, completed the study. Demographic details of the patients are listed in Table 1. In the study group, one patient had a permanent pacemaker, one had type 2 diabetes and one had thalassemia minor. One patient in the placebo group had glaucoma. All other patients were healthy, except for Crohn's disease.
Twenty patients had been treated with thiopurines and 18 with anti-TNF-α in the past. Of the 18 treated with anti-TNF-α, 5 had to stop treatment due to a severe allergic reaction, 4 were still receiving anti-TNF-α, 7 did not respond or lost response after at least a full induction dose, 1 stopped treatment despite being effective and 1 stopped due to pneumonia. At the time of the study, 4 patients (3 in the study group and 1 in the placebo group) were steroid dependent. One patient received prednisone 20 mg for 2 years, one prednisone 35 mg for 6 months and two received budesonide 9 mg for 2 and 3 years each.

They all relapsed as soon as they tried to stop the steroids. In patients who had undergone surgey, time from previous surgery to the study was on the average 6 years (range 1-30 years).

Five patients (45%) in the study group, and one (10%) in the placebo group achieved full remission, with a CDAI ≤ 150 (Figure 1). This difference did not reach statistical significance (p=0.43), possibly due to the small sample size. Before treatment, the mean CDAI was 330 ± 105 and 373 ± 94 in the study and placebo groups, respectively (p = 0.3). After 8 weeks of treatment, the CDAI dropped to 152 ± 109 in the study group, and 306 ± 143 in the placebo group (p between groups <0.05). The response rate (i.e CDAI reduction of more than 100 points) was 90% (10/11) in the study group, whereas in the placebo group the CDAI increased in 3 (30%) patients, decreased by less than 100 points in 3 (30%) patients, and decreased by more than 100 points in 4 (40%) patients. The mean reduction in CDAI was 177 ± 80 in the study group and 66 ± 98 in the placebo group (p=0.005). Two weeks after cannabis treatment was stopped, the mean CDAI in the study and placebo groups was 331±155 and 280±61, respectively (p=0.43; Figure 1).

Four patients in the placebo group (but none in the cannabis group) deteriorated and needed rescue intervention during the study period. Three of these four patients stopped taking their assigned study treatment because they felt it was not helping them. Three steroid dependent patients in the cannabis group stopped steroids during the study. Thus, at the end of the study no patient in the cannabis group required steroids. Two patients in the study group, who were treated with opiates due to severe chronic abdominal pain, stopped opiates during the study.

A significant increase in quality of life as assessed by SF-36 was observed in the cannabis group (from 68 at week 0 to 86 after 8 weeks of treatment, p=0.05), while no effect was observed in the placebo group (SF-36 = 71 vs. 79, p=0.5). The delta of SF-36 between the baseline measurement and after 8 weeks was +28 and +5 in the study and placebo groups, respectively (p=0.04). There were no significant changes in blood count, CRP or liver and kidney function during the study (Table 3). CRP before treatment was 1.4±2 mg/dl and 2.6±2.5 mg/dl (normal <0.5 mg/dl) in the cannabis and placebo groups,

respectively (p=0.1). A decrease in CRP of more than 0.5 mg/dl from week 0 to week 8 was observed in 3 patients in the study group and 2 in the placebo group (p=0.43).

There was no difference between study and placebo groups in side effects, including sleepiness, nausea and confusion. However, the study group reported significantly less pain, improved appetite and a higher satisfaction from the treatment (Table 4). Patients denied any withdrawal symptoms when stopping cannabis use at the end of the study. Blinding assessment was done at the end of the study for each patient. Except for 2 patients in the placebo group, all other patients were able to tell correctly whether they were receiving cannabis or placebo.

Discussion

Although a significant body of work suggests that cannabinoids suppress inflammation [14] and many patients with IBD self-medicate with cannabis, there are no placebo-controlled trials assessing its efficacy in inflammatory disease. This might be due to reluctance to use an illegal drug. To the best of our knowledge, this is the first placebo-controlled trial to assess critically cannabis use for treating Crohn's disease.

The primary endpoint of this study was induction of remission. Although five patients in the study group and one in the placebo group entered clinical remission, the difference did not reach statistical significance, possibly due to the small sample size. However, our data show that 8-weeks treatment with THC-rich cannabis, but not placebo, was associated with a significant decrease of 100 points in CDAI scores.

In this trial, cannabis induced clinical remission in 50% of patients. Taking into account that our participants had longstanding Crohn's disease, with 80% nonresponse or intolerance to Anti-TNF-α, this result is impressive. In this trial, the observed improvement was solely symptomatic, with no objective evidence of reduction in inflammatory activity. In addition, patients relapsed 2-weeks after cannabis treatment was stopped. Therefore, based on the available data, one cannot argue that cannabis is a successful treatment for the inflammatory process in Crohn's disease. Thus, until further studies are

conducted, cannabis should be reserved for compassionate use only in patients who have exhausted all other medical and surgical options.

Prior to this was a pilot study, probable efficacy data were unavailable, therfore power calculation could be based on estimation only. With a significance level of 5% and a power of 80% to detect a significant difference of 100 points in CDAI we would need a sample size of 12 patients in each group, or a total of 24 patients.

Herbal preparations present problems in measuring the contribution of each constituent of a mixture. Thus, mistakes can be made in using non-standardized extracts for clinical testing. We dealt with this problem by using cannabis made from genetically identical plants grown from twigs of the same mother plant and in equal conditions. Plants were tested to verify an equal content of active ingredients. We also standardized the machine made cigarettes to contain equal weights of cannabis flowers.

Although this was a placebo-controlled trial, complete blinding of patients was not easy to achieve because of possible psychotropic effects. We tried to minimize this limitation by recruiting only patients naïve to cannabinoinds. However, at the end of the study period, most of the subjects were able to tell correctly whether they were receiving the study drug or placebo. Future studies with oral administration may overcome this problem due to slower absorption.

In this study, we chose to administer cannabis by smoking, because this route induces a rapid increase in blood cannabinoid levels [17]. During smoking, the acids are decarboxylated to the active free cannabinoids, which may explain why ingesting cannabis orally is less effective than smoking [18]. Nevertheless, due to the known harmful effects of smoking on the lungs, the efficacy and safety of oral cannabis should be further investigated.

There is an understandable restraint in the medical community regarding the use of cannabis, which is an illegal drug in most countries. Yet, cannabis has a remarkably good safety profile [19, 20]. In this study, during short-term use of 8 weeks we did not observe any significant side effects. All patients continued normal function and did not report significant differences in behavioral parameters such as concentration, memory or confusion. Indeed, it is known that tolerance to the central effect of cannabis

develops after 12 days of use [21]. When requested to stop cannabis after 8 weeks, none of the patients experienced difficulty or withdrawal symptoms. All patients in the study group expressed strong satisfaction with their treatment and improvement in their daily function. It should, however, be noted that our patients were treated for only a short period. It is well known that cannabis dependence exists and patients might be difficult to wean from prolonged cannabis use, even when the IBD is in complete remission. Therefore, until further data are available, long term medical cannabis could not be recommended. Although the long-term side effects of cannabis are not negligible, other treatments for Crohn's disease, such as steroids, purine analogs or anti-TNF-α also carry the risk of significant side-effects, some even life threatening. Additional studies will be needed before the exact effect of cannabis in IBD, whether anti-inflammatory or only symptomatic, can be determined. However, the potential benefits should not be ignored only because of concern for possible side effects. Taking into account that Crohn's disease is a chronic, debilitating disease that may sometimes severely compromise patients' quality of life, the ability to provide symptomatic relief judicially, in carefully selected patients should not be overlooked.

In summary, in this controlled pilot study, cannabis treatment was not superior to placebo in induction of remission. However, cannabis provided a significantly higher rate of clinical response without any alarming side-effects The strain of cannabis used was specifically rich in THC, but other cannabinoids may be beneficial as well. Future larger controlled studies should look into the role of cannabinoids in controlling inflammation and symptoms in IBD.

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Table 1: Demographic data

Variable	Study group N = 11	Placebo group N = 10	P-value
Age	46 ± 17	37±11	0.02
Male	6 (54%)	6 (60%)	0.57
Family history of IBD	5 (45%)	5 (50%)	1
Current tobacco smoking	2 (18%)	3 (30%)	0.65
Time from diagnosis of Crohn's disease (years)	18 ±14	15 ± 8	0.797
Involved segment of intestine*			
Terminal ileum	8 (72%)	5 (50%)	0.38
Colon	4 (36%)	4 (40%)	0.6
Other part of small intestine	3 (27%)	2 (20%)	1
Disease phenotype			
Luminal	36% (4)	60% (6)	0.39
Fistulizing	45% (5)	20% (2)	0.36
Stricturing	18% (2)	20% (2)	1
Past surgery			
Resection of terminal ileum	45% (5)	60% (6)	0.66
Partial colectomy	9% (1)	10% (1)	0.7
Adhesiolysis	9% (1)	0% (0)	1

Mean ± SD,(n) %

*one patient might have involvement of more than one segment

Table 2: Past and current medical treatment

	Past medication **Number (%)**			**Concomitant medication** **Number (%)**		
Medication	Study (N = 11)	Placebo (N = 10)	P-value	Study (N = 11)	Placebo (N = 10)	P-value
5 ASA	11 (100)	10 (100)	NS	2 (218)	2 (20)	0.7
Steroids	11 (100)	9 (90)	0.4	4 (36) (3 steroid dependent)	2 (20) (1 steroid dependent)	0.9
Purine analog	10 (90)	10 (100)	NS	2 (27)	6 (60)	0.9
Methotrexate	3 (27)	1 (10)	0.9	1 (9)	0	1
Anti-TNF-α	9 (81)	8 (80)	0.7	1 (9)	4 (40)	0.9

Table 3: Laboratory tests

Test	Study (11)			Placebo (10)		
	Start	End	P-value	Start	End	P-value
Hemoglobin (g/dl)	12.8±1	13.0 ±1.3	0.3	12±1	12±2	0.6
HCT (%)	39.4±3	35.1±4	0.3	38±5	37±6	0.6
WBC (K/microl)	8±3	8.2±3	0.9	6.1±2	5.7±2	0.7
CRP (mg/dl)	1.44±2	0.99±0.9	0.4	2.6±2.5	1.7±0.7	0.2

Table 4: Side-effects

	Placebo Median (min-max)	**Cannabis** Median (min-max)	**P-value**
Negative side effects*			
Sleepiness	4 (3-4)	3 (1-6)	0.5
Nausea	4 (3-4)	4 (1-4)	0.3
Concentration	4 (4-5)	4 (4-7)	0.3
Memory loss	4 (4-4)	4 (4-6)	0.4
Confusion	2 (2-2)	2 (1-2)	0.4
Dizziness	2 (1-2)	2 (1-2)	0.9
Positive side effects**			
Pain	4 (3-4)	1 (1-2)	0.001
Appetite	4 (4-4)	2 (1-4)	0.008
Satisfaction	7 (3-7)	1 (1-4)	0.002

*On a scale from 1 to 7, where 1= no effect; 7=very strong effect

**On a scale from 1 to7, where 1=very satisfied; 7= very dissatisfied

Figure 1: Crohn's Disease Activity Index (CDAI) scores in study and placebo groups before and after treatment

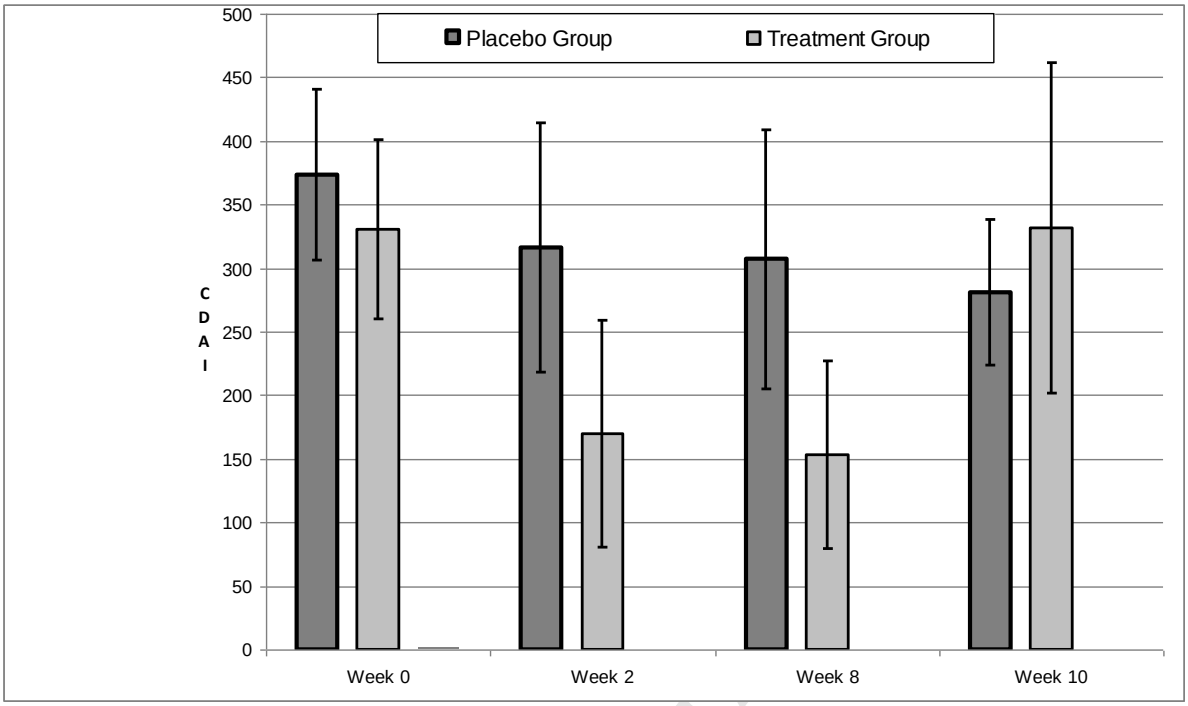
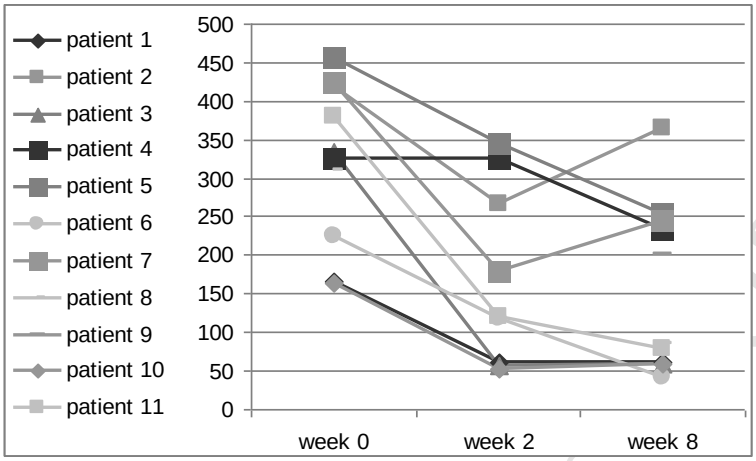
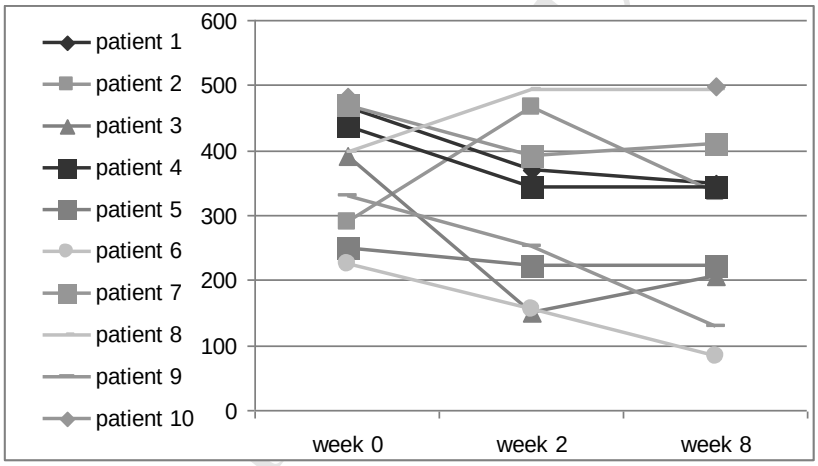


Figure 2: Crohn's Disease Activity Index scores of individual patients in study and placebo groups before and after treatment



Study group



Placebo group