

# Cannabis in Inflammatory Bowel Diseases: from Anecdotal Use to Medicalization?

Timna Naftali MD and Fred M. Konikoff MD

Institute of Gastroenterology and Hepatology, Meir Medical Center, Kfar Saba, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Inflammatory bowel diseases (IBD) are disorders of chronic intestinal inflammation of unknown etiology. The basic pathophysiological process is that of immune mediated inflammation affecting the intestinal tract. This process is dependent on and governed by both genetic and environmental factors. There are two distinct forms of IBD – ulcerative colitis and Crohn's disease. While ulcerative colitis affects only the colon, with superficial inflammation of the mucosal layer only, Crohn's disease causes transmural inflammation which may involve any part of the gastrointestinal tract [1,2].

The clinical manifestations may be quite variable, but both disorders run a chronic course of alternating exacerbations and remissions. Symptoms include abdominal pain and diarrhea, often with blood, especially when the colon is involved. Importantly, there is an increased risk of cancer of the involved organs. Both disorders may also involve extra-intestinal organs, such as the skin, joints and eyes, as well as the skeletal or hepatobiliary systems [3].

The treatment of IBD focuses on ameliorating the inflammatory process. This includes anti-inflammatory agents, such as 5-aminosalicylic acid. Since bacterial infections may be involved primarily or secondarily, antibiotics are also often used. In most cases, patients will need a variety of immunomodulatory therapies, such as corticosteroids, thiopurines or methotrexate. More recently, therapeutic options have widened to include biological agents. These monoclonal antibodies target specific cytokines, which are active in the inflammatory process [4].

Despite the relatively wide spectrum of therapeutic agents, the medical response remains incomplete. Corticosteroids, the most potent agents, achieve a remission rate of up to 80%, but due to significant side effects cannot be used for long-term maintenance [5]. Most other immunomodulators as well as biological therapies provide a remission rate of 50–60% only, and there is no curative medical treatment. Furthermore, over

30% of patients, and over 70% with Crohn's disease, will need surgical intervention for their disease [6].

Thus, it comes as no surprise that many patients will turn to complementary or alternative medicine at some stage of their disease. Recent information reveals that between 16% and 50% of patients admit to having tried marijuana for their symptoms [7]. There is a long list of gastrointestinal symptoms that have been reported to be relieved by cannabis. These include anorexia, nausea, abdominal pain, diarrhea, gastroparesis – all of which can be part of IBD [8]. These effects are related to the fact that the gastrointestinal tract is rich in cannabinoid (CB) receptors and their endogenous ligands, comprising together the endocannabinoid system (ECS). CB1 receptors can be found predominantly in the enteric nervous system and the epithelial lining. Additionally, CB1 is found in extrinsic fibers of the enteric nervous system, plasma cells, and in smooth muscle cells of blood vessels within the colonic wall [9]. CB2 receptors are mainly present in immunocytes, myenteric plexus neurons, and in epithelial cells during ulcerative colitis [9]. The ECS participates in the regulation of gastrointestinal motility, secretion, inflammation and the maintenance of the epithelial barrier integrity [9,10]. Functionally, endocannabinoids have been shown to decrease intestinal hypermotility and hypersecretion and to modulate intestinal inflammation and permeability [11]. The phytocannabinoids, mainly  $\Delta^9$ tetrahydrocannabinol (THC) and cannabidiol (CBD), exert their effect via the ECS, and many studies have shown them to be beneficial in inflammation outside and within the gastrointestinal tract. Both synthetic and endogenous cannabinoids inhibit lipopolysaccharide-induced release of tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) from microglial cells [12]. In a mouse model of trinitrobenzene sulfonic acid (TNBS)-induced colitis, intraperitoneal treatment with CBD led to the amelioration of colonic inflammation [13]. In another study of TNBS colitis in mice, THC and CBD not only reduced inflammation but also protected cholinergic nerves, reversing motility disturbances caused by inflammation. The effects of these phytocannabinoids were additive [14]. In another model of chronic colitis in IL-10 knockout mice, the cannabinoid receptor-2 (CB2) agonist JWH-133 effectively attenuated colitis score [15]. Other phytocannabinoids such as cannabigerol (CBG) were also shown to be effective in ameliorating experimentally induced colitis [16].

It is against this background, paralleled with increasing patient demand for prescriptions of medical cannabis that we became interested in the potential role of cannabis and cannabinoids in IBD. Surprisingly, a PubMed search in 2009 of cannabis in human IBD yielded a result of no (zero) publications. This prompted us to undertake an observational study of the use of cannabis in IBD in Israel. For this purpose, we obtained a list of licensed users of Medical Cannabis within the database of Tikun Olam, a company that grows and supplies medical cannabis by license of the Ministry of Health. We found 30 patients with the diagnosis of Crohn's disease, who we contacted and interviewed for clinically relevant data. Most patients smoked cannabis as "joints" (0.5 g cannabis/joint) and used between one and three joints/day. The Harvey-Bradshaw index (indicating disease activity) decreased from an average of  $14 \pm 6.7$  before cannabis consumption to  $7 \pm 4.7$  ( $P < 0.001$ ). The use of other medications, including 5-ASA, corticosteroids, thiopurine, methotrexate, and TNF antagonists also appeared to be significantly reduced following the use of cannabis. Fifteen of the patients had 19 surgeries during an average period of 9 years before cannabis use, but only 2 required surgery during an average period of 3 years of cannabis use [17].

These results prompted us to conduct the first randomized placebo-controlled trial of cannabis in Crohn's disease [18]. The study included 21 active Crohn's disease patients who received cannabis cigarettes containing 23% of THC or placebo for 8 weeks. Complete remission (Crohn's Disease Activity Index, CDAI, score  $< 150$ ) was achieved by 5/11 subjects in the cannabis group (45%) and 1/10 in the placebo group (10%,  $P = 0.43$ ). A clinical response (decrease in CDAI score  $> 100$ ) was observed in 10/11 subjects in the cannabis group (90%, from  $330 \pm 105$  to  $152 \pm 109$ ) and 4/10 in the placebo group (40%, from  $373 \pm 94$  to  $306 \pm 143$ ,  $P = 0.028$ ). However, in another randomized placebo-controlled study, low dose cannabidiol alone given to 19 Crohn's disease patients did not show a beneficial effect [19]. The average CDAI before CBD consumption was  $337 \pm 108$  and  $308 \pm 96$  ( $P = \text{NS}$ ) in the CBD and placebo groups, respectively. After 8 weeks of treatment the index decreased to  $220 \pm 122$  in the CBD group and  $216 \pm 121$  in the placebo group ( $P = \text{NS}$ ). No side effects were observed [20]. It should be noted that this study used a very small dose of 10 mg/day, whereas several studies of cannabidiol in a variety of human diseases used a dose range of 200–800 mg/day.

These human studies are, however, limited by both the small number of patients and the fact that inflammatory activity was not measured before and after cannabis. We therefore initiated two additional randomized placebo-controlled studies. The first looks into the use of cannabis oil, rich in CBD, in Crohn's disease. Outcome measures include inflammatory markers, such as calprotectin and CRP, as well as endoscopic evaluation before and after treatment. The second study assesses the effect of cannabis smoking on ulcerative colitis, measuring inflammatory markers and endoscopic scoring, as well as clinical

indices. We hope that these studies will enable us to better define the role, if any, of cannabis in the treatment of IBD.

The clinical improvement reported by cannabis users could be attributed to euphoria and a sense of general well-being induced by cannabis, or it could be the result of a direct anti-inflammatory effect. Based on the numerous studies showing a beneficial effect of cannabinoids in experimental models of IBD, we are anticipating that reduction in inflammation will be observed. However, in view of the known connection between stress and exacerbation of IBD [21], it is also possible that cannabis ameliorates disease by reducing anxiety and tension.

Use of cannabis by patients naturally raises a host of safety concerns. Information about patterns of use, dosage, side effects and effects on patients' function is limited. We therefore conducted a survey of 127 IBD patients who use cannabis regularly. Patients were asked to fill out questionnaires on their patterns of use, the dose, the effect on well-being, disease activity and side effects. We also looked at the employment status of patients before and after cannabis use. Addiction trait was assessed by the criteria defined in DSM-IV. The average age of the patients was 39.6 years, 86 were males, and 107 had Crohn's disease with an average duration of disease of 14 years. The mean duration of cannabis use was 38 months (range 2–126 months). Most patients maintained a stable dose of cannabis throughout that period with an initial dose of  $28 \pm 16$  g/month and a final dose of  $31 \pm 15$  g/month. The mode of use was smoking in 72%. Half the patients (51%) were fully employed before starting cannabis and their employment status was increased to 64% while using cannabis. Side effects were minor, and included dry mouth in 62 patients (48%) and eye irritation in 13 (10%). Memory impairment was mentioned by 33 patients (25%), but it did not seem to compromise any activity [22].

In conclusion, use of cannabis is common in IBD, and it seems to be mostly safe. Accumulating preliminary data from human studies support a beneficial role of cannabinoids in IBD. Whether the effect is anti-inflammatory, central or other remains speculative at this stage. Despite active interest within the gastroenterology community following our initial randomized controlled trial (RCT) of cannabis in CD, it still remains the sole RCT published. Thus, additional controlled trials in larger patient populations are clearly needed. These should focus on optimizing delivery mode and dosage, as well as evaluating clinical efficacy. Data should be correlated with experimental laboratory data. Hopefully, these will lead to the identification of the effective cannabinoid(s) for clinical use. Last, but not least, careful monitoring of the effects and side effects in patients within studies as well as out of studies remains crucial.

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## Correspondence

### Dr. T. Naftali

Institute of Gastroenterology and Hepatology, Meir Hospital, Kfar Saba  
44281, Israel

Phone: (972-9) 747-2473

Fax: (972-9) 747-2725

email: timna.naftali@clalit.org.il, fred.konikoff@clalit.org.il

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