Cannabis for Inflammatory Bowel Diseases: Should We Follow the Wisdom of the Crowd?

Timna Naftali 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 chronic debilitating inflammatory diseases affecting the gastrointestinal tract. Crohn's disease may affect any part of the gastrointestinal tract, and the inflammation may penetrate through the bowel wall into the abdominal cavity. Ulcerative colitis, however, will solely affect the large intestine and the inflammation is limited to the superficial epithelial layer of the bowel wall. Despite the progress made in the treatment of IBD in the last decades, response to treatment is still limited to only 40–60% of patients, with 30% requiring surgery [1]. Consequently, many patients turn to alternative medicine, including medical cannabis.

THE ROLE OF CANNABINOIDS IN GUT INFLAMMATION

The endocannabinoid system is an important homeostatic system regulating modulation of neuroprotection, pain, emotional memory, hunger, feeding, lipid metabolism [2] and, most importantly in the context of IBD, inflammation [2]. The system consists of the endocannabinoid ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The corresponding receptors for these ligands: cannabinoid receptors 1 (CB1), 2 (CB2), and probably other less well-characterized receptors. In addition, there are enzymes that synthesize the endocannabinoids: diacylglycerol lipase (DAGL) for AEA and N-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) for 2AG. Last, the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are responsible for the degradation of endocannabinoids [3].

Phytocannabinoids exert their effect by activating the endocannabinoid system. Thousands of years ago the cannabis plant was recognized in traditional healing for its beneficial effect in reducing pain and diarrhea. The plant contains as many as 100 cannabinoids, but the most abundant and well known are tetrahydrocannabinol (THC) and cannabidiol (CBD). Whereas THC has a profound central effect inducing euphoria and analgesia, CBD acts peripherally and has an anti-inflammatory effect. It is believed that the cumulative effect of the cannabinoids is synergistic so that different plants with different cannabinoid combinations will have different effects [4]. Many studies performed in various ex vivo models of IBD demonstrated that cannabinoids ameliorate the inflammatory process [5]. Cannabinoids were shown, among other things, to prevent dinitrobenzene sulfonic acid-induced colitis in mice, to promote epithelial wound healing, and to improve motility disturbances [5]. Therefore, it is quite surprising that there are few studies regarding the effect of cannabis in human IBD, and those that exist are small.

PREVALENCE OF CANNABIS USE AMONG IBD PATIENTS

Cannabis started to gain publicity as an effective and legitimate medical treatment with the publication of case reports, not necessarily in the medical literature, describing improvement of various medical conditions by the use of cannabis. Two such case reports are published in the current issue of *IMAJ* [6,7], describing marked improvement in the alertness of a demented patient when he was treated with cannabis. Despite the wide publicity and media attention devoted to cannabis medical use, there are very few scientifically sound studies regarding the therapeutic use of cannabis. In IBD specifically, many studies investigated the prevalence of cannabis use among IBD patients, but only few looked at the clinical effect. The prevalence of cannabis use in patients with IBD was reported to be between 15–40%, Ravikoff et al. [8] reported that 15% of 292 patients were active cannabis users. Patients claimed that marijuana was "very helpful" for relief of abdominal pain, nausea, and diarrhea [8]. In a much larger study, Weiss and Friedenberg [9] compared 2 million IBD patients with 2 million matched controls, and found that subjects with IBD had a higher incidence of ever using cannabis (67% vs. 60%) with an onset of use at an earlier age and a tendency to use larger amounts.

EFFECT OF CANNABIS USE IN IBD

Lal et al. [10] looked at the effect of cannabis use as reported in questionnaires. Patients reported improvement in pain and appetite and reduction in the need for other medications. The effect of cannabis on the prevalence of complications caused by Crohn's disease was investigated by Mbachi et al. [11]. They found that cannabis users were less likely to develop active fistulizing disease, intraabdominal abscess, need for blood transfusion, colectomy, and need for parenteral nutrition. Unfortunately, they also observed that the prevalence of concurrent psychiatric diseases was

significantly higher among cannabis users. A similar study in hospitalized UC patients was performed by the same group. The study included a total of 298 cannabis users with UC who were compared to a propensity score-matched group of nonusers including 39,802 patients. The prevalence of partial or total colectomy was lower in cannabis users compared to nonusers (4.4% vs. 9.7%, $P = 0.010$) and there was a trend toward a lower prevalence of bowel obstruction (6.4% vs. 10.7%, $P = 0.057$). Cannabis users had shorter hospital length-of-stay (4.5 vs. 5.7 days $P < 0.007$) [12].

RANDOMIZED CONTROLLED STUDIES

Randomized controlled studies (RCT) regarding cannabis use in IBD are few and small. We performed a preliminary double-blind, placebo controlled study of cannabis use in Crohn's disease in which 21 patients were randomized to receive either cigarettes containing 11.5 mg of THC or placebo [13]. A decrease in Crohn's disease activity index (CDAI) of more than 100 was observed in 10/11 (90%) subjects in the cannabis group but only 4/10 (40%) in the placebo group ($P = 0.028$). Yet, we did not observe changes in objective markers such as CRP. A similar study using oral 10 mg CBD twice daily in Crohn's disease was negative. Only 19 patients completed the study, and after 8 weeks of treatment, the CDAI was 220 ± 122 and 216 ± 121 in the CBD and placebo groups, respectively (P = NS) [14]. Irving et al. [15], in a double-blind placebo-controlled study, assessed the efficacy of a capsule containing 50 mg of CBD-rich botanical extract, (also containing 4% THC) in 60 ulcerative colitis patients. Remission rates were similar for CBD (28%) and placebo (26%). The study drug was poorly tolerated, with only 59% protocol compliance, but when performing a per-protocol analysis of the partial and the total Mayo scores, the investigators found a significant difference in favor of the study drug ($P = 0.068$ and 0.038, respectively).

Another study conducted in 30 active UC patients randomized to either cannabis cigarettes (23 mg THC/day) or placebo showed that after 8 weeks, the mean disease activity index in cannabis participants was 4 compared to 8 in the placebo group (P between groups 0.001) [16]. Two Cochrane reviews based on the available studies concluded that currently, the evidence is not sufficient to support the claim that cannabis is beneficial in IBD [17,18].

DOSE AND MODE OF CONSUMPTION

One of the inherent difficulties in the evaluation of cannabis use is the wide variety of cannabis strains, with different content of THC and CBD, as well as different contents of other ingredients believed to play a role in the effect induced by cannabis such as terpenes and flavinoids. Furthermore, different modes of consumption such as smoking, vaping or oral ingestion lead to a different bioavailability and hence to a different effect. Only a few studies report the dose and mode of consumption of cannabis. We followed 127 IBD patients who were cannabis users and found that the average Harvey-Bradshaw index improved from 14 ± 6.7 to 7 ± 4.7 ($P < 0.001$) during a median follow-up of 44 months. The average dose used by the patients was 31 ± 15 g/month [19]. Stith and colleagues [20] used mobile device software to collect data from 3341 cannabis users affected with several diseases and looked at the dose used by the patients. They found that the amount of THC, but not of CBD, was associated with greater symptom relief.

CONCLUSIONS

Despite the profound pre clinical evidence on the effect of cannabis in IBD, data about human use is still lacking. Most data are derived from retrospective observational studies, with very limited data about the effect of cannabis on IBD disease activity and on the dose and mode of consumption. Nevertheless, cannabis enjoys an anomalous status whereby regulatory authorities around the world permit it's use not only for IBD but for many other medical conditions, ignoring the lack of evidence to support this policy. The confusion created by the discrepancy between the paucity of sound evidence regarding the efficacy of cannabis treatment, and the legitimization and encouragement of cannabis treatment is well reflected in the study by Zolotov et al. in this issue of *IMAJ* [7]. In this study physicians participated in a survey describing various situations and evaluating the opinion of the participating physicians about the appropriateness of cannabis treatment in each situation. The authors suggested that these vignettes could be used in further training the medical community about the use of medical cannabis.

By suggesting that decision making about cannabis treatment could be based on this form of wisdom of the crowd, Hermush [6] and Zolotov [7] and colleagues emphasized the difficulty of the situation, whereby a drug is first approved for use and only then is the appropriate research about the efficacy of that drug started. Further good quality studies are urgently needed to conclude whether cannabis has a therapeutic role in the treatment of IBD as well as many other medical conditions.

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: timnanaftali@gmail.com; timna.naftali@clalit.org.il

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Capsule

Some naïve T cell fates are sealed

Tissue-resident memory T (T_{RM}) cells constitute a subpopulation of memory cells that reside in tissues instead of recirculating. $CD8^+$ epithelial TRM (eT_{RM}) cells, which occupy the epithelium of sites like the skin, require transforming growth factor-β (TGF-β) for their development. **Mani** and colleagues found that integrin-expressing dendritic cells, which activate and present TGF-β, are key. Surprisingly, this interplay did not occur in the skin or draining lymph nodes during T cell priming. Rather, resting naïve $CD8^+$ T cells interacted with α_V integrin-expressing migratory dendritic cells during immune homeostasis, reversibly preconditioning them to become eT_{RM} cells upon activation. A potent cytokine is thus controlled in a context-dependent manner and preimmune T cell repertoires may be less uniform than previously presumed.

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Eitan Israeli

Capsule

Tumor necrosis factor blocking agents reduce risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis

This large, retrospective case-control study of electronic health records from 56 million unique adult patients examined whether or not treatment with a tumor necrosis factor (TNF) blocking agent reduced risk for Alzheimer's disease (AD) in patients with rheumatoid arthritis (RA), psoriasis, and other inflammatory diseases, which are mediated in part by TNF and for which a TNF blocker is an approved treatment. **Zhou** et al. compared the diagnosis of AD as an outcome measure in patients receiving at least one prescription for a TNF blocking agent (etanercept, adalimumab, and infliximab) or for methotrexate. RA increased the risk for AD (adjusted odds ratio [AOR] 2.06, 95% confidence interval [95%CI] 0.02–2.10, $P < 0.0001$) as did psoriasis (AOR 1.37, 95%CI 1.31–1.42, $P < 0.0001$), ankylosing spondylitis (AOR 1.57, 95%CI 1.39–1.77, $P < 0.0001$), inflammatory bowel disease (AOR 2.46, 95%CI 2.33–2.59, $P < 0.0001$), ulcerative colitis (AOR 1.82, 95%CI 1.74–1.91, $P < 0.0001$), and Crohn's disease (AOR 2.33, 95%CI 2.22–2.43, $P < 0.0001$). The risk for AD in patients with RA was reduced by treatment with etanercept (AOR 0.34, 95%CI 0.25–0.47, $P < 0.0001$), adalimumab (AOR 0.28, 95%CI 0.19–0.39, $P < 0.0001$), and infliximab (AOR 0.52, 95%CI 0.39–0.69), $P < 0.0001$). Methotrexate also reduced risk for AD (AOR 0.64, 95%CI 0.61–0.68, $P < 0.0001$), while further risk reduction was achieved in patients with a prescription history for both a TNF blocker and methotrexate. Etanercept and adalimumab also reduced the risk for AD in patients with psoriasis (AOR 0.47, 95%CI 0.30–0.73; and AOR 0.41, 95%CI 0.20–0.76, respectively). There was no effect of gender or race, while younger patients showed greater benefit from a TNF blocker than did older patients. This study identifies a subset of patients in whom systemic inflammation contributes to risk for AD through a pathological mechanism involving TNF and who therefore may benefit from treatment with a TNF blocking agent.

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Eitan Israeli