ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Use of Medical Cannabis in Patients With Inflammatory Bowel Disease

Jami Kinnucan, MD
Assistant Professor of Medicine
Michigan Medicine, University of Michigan
Ann Arbor, Michigan

G&H What is the current legal status of cannabis?

JK As of March 2018, 9 US states have legalized cannabis (also known as marijuana) for recreational use and 22 US states have legalized cannabis for medical use. Fourteen additional states have legalized cannabis strains with a high cannabidiol (CBD) to low delta-9-tetrahydrocannabinol (THC) ratio (which is thought to have less psychoactive effects). A total of 13 states have moved to decriminalize cannabis, but not legalize it. (The definition of decriminalization varies from state to state.)

G&H In which disease states has medical cannabis been studied?

JK An international survey from the World Health Organization found that medical cannabis has been primarily studied and utilized for chronic back pain, sleep disorders, depression, injury-related pain, and multiple sclerosis. The more robust data on the use of medical cannabis, in the form of randomized, controlled trials, come from the study of patients with neuropathic pain, chronic pain, or multiple sclerosis. There are also limited data in patients with glaucoma, HIV and AIDS cachexia, cancer-related symptoms (nausea and vomiting), and posttraumatic stress disorder. In addition, significantly smaller studies have been conducted in the setting of Crohn's disease and ulcerative colitis.

G&H What is the rationale for using medical cannabis to help manage inflammatory bowel disease?

JK There is currently a large unmet need in the treatment of inflammatory bowel disease (IBD) with conventional medical therapy. Despite improvement in disease activity, many patients have persistent clinical symptoms that have significant impact on their quality of life. Patients have been seeking out alternative therapies (including cannabis) to help manage persistent symptoms associated with IBD.

Cannabis, which comes from the plant *Cannabis sativa*, is composed of hundreds of compounds and over a hundred cannabinoids (including THC and CBD, which are the most well known). Cannabinoids interact with the endocannabinoid system through endocannabinoid receptors. The most-studied receptors, CB1 and CB2, are expressed in the gastrointestinal tract, enteric nervous system, brain, and immune cells, which are areas of interest in patients with IBD. Activation of these receptors may result in gastrointestinal effects. A 2009 study in a mouse model of colitis found that when the CB1/CB2 receptors were activated, there was a decrease in inflammation. This provides a potential rationale as to the role of cannabis in the management of IBD and IBD-related symptoms.

G&H Currently, how common is medical cannabis use in IBD patients?

JK Surveys of cannabis use in IBD patients in the United States and Canada have found that approximately 15% to 20% of patients currently use cannabis, and up to 40% have tried cannabis to relieve IBD symptoms. These retrospective studies have shown that patients are using cannabis for improvement in pain, appetite, and diarrhea.

In these studies, patients have used cannabis by both oral and inhalation routes.

G&H What have studies reported regarding symptom improvement with the use of medical cannabis in patients with Crohn's disease and ulcerative colitis?

JK There have been a few small retrospective, prospective, and randomized, controlled studies that have looked at the effects of medical cannabis use in both Crohn's disease and ulcerative colitis. A survey-based study in cannabis users with IBD in the United States noted that cannabis use was associated with an improvement in abdominal pain, appetite, nausea, and diarrhea. In a prospective pilot study, IBD patients who were using medical cannabis as needed for pain control experienced improvements in pain, general health perception, social functioning, ability to work, and symptoms associated with IBD. Although patients in this study reported weight gain, there was no change in C-reactive protein (CRP) measurements. Further studies have assessed both symptom improvement as well as efficacy of treatment in IBD.

G&H Have any studies shown that medical cannabis use can improve Crohn's disease activity?

JK Several small studies have attempted to address this question. The first small observational study in Crohn's disease (N=30) was conducted by Naftali and colleagues in Israel in 2011. The researchers found that medical cannabis use was associated with a decrease in subjective disease activity scores and a reduced need for corticosteroid therapy. However, concerningly, the majority of patients discontinued conventional medical therapy while using medical cannabis.

This study led to further investigation by Naftali and colleagues in the form of the first randomized, controlled trial of medical cannabis in Crohn's disease (N=21), the results of which were published in *Clinical Gastroenterology & Hepatology* in 2013. The study found that smoking 2 cannabis cigarettes per day for 8 weeks was associated with significant improvement in Crohn's Disease Activity Index (CDAI) scores compared to patients who were on placebo. Clinical remission was seen in 45% of patients on daily cannabis, and 25% were able to stop corticosteroid therapy. However, despite overall improvement in clinical symptoms in the cannabis group, the study failed to meet its primary endpoint of clinical remission (ie, a CDAI <150). Cannabis use was not associated with an improvement in objective disease markers (hemoglobin and CRP). Similar to previous retrospective research, cannabis use in this study was associated with improved overall satisfaction, quality-of-life scores, pain scores, and appetite.

In their most recent follow-up research, Naftali and colleagues performed a placebo-controlled study to examine low-dose oral CBD in patients with medically refractory Crohn's disease (N=19). This study was the first to look at a single-compound oral formulation in IBD patients. The study had negative findings, as there was no improvement in CDAI or laboratory parameters when compared to placebo. However, there were no adverse effects in the treatment group when compared to placebo. This study highlighted the possible differences in cannabis formulations and routes and their impact on clinical improvement.

G&H Have there been similar studies looking at the efficacy of medical cannabis in patients with ulcerative colitis?

JK The initial studies were done in Crohn's disease, and, since then, there has only been 1 published study examining the effects of medical cannabis in patients with ulcerative colitis. Irving and colleagues assessed the efficacy, safety, and tolerability of once-daily oral CBD-4% THC (CBD-rich extract) for 10 weeks in patients with active ulcerative colitis (N=60) as an adjuvant therapy while on stable dosing of mesalamine therapy. Patients were less tolerant to the CBD-rich extract than placebo, and there were significant protocol deviations in the study. Both groups failed to reach the primary endpoint of clinical remission, and there were no differences in the rates of remission between the groups (28% for the CBD-rich extract and 26% for placebo). Per-protocol analysis showed improvement in patient's global impression of change and a trend toward improved quality-of-life scores with CBD-rich extract use.

More recently, unpublished data were presented by Naftali and colleagues at this year's Digestive Disease Week. They evaluated the effects of smoking 2 cannabis (THC-rich) cigarettes daily or placebo for 8 weeks in patients with moderate to severe ulcerative colitis (N=28). The authors assessed both clinical outcomes and objective outcomes (laboratory evaluation and endoscopic evaluation). In this study, medical cannabis use was associated with improved clinical disease activity scores and endoscopic improvement (reduction of Mayo endoscopic subscore from 2 to 1; $P<.01$). However, there was no significant change in CRP or fecal calprotectin in either group. No serious side effects were observed during the treatment period, but the authors reported a higher rate of memory decline in the cannabis group.

G&H Are there any concerns with the short- or long-term use of medical cannabis?

JK The long-term effects have not been well studied in an IBD population. However, a 2014 study published in *The New England Journal of Medicine* identified several long-term risks associated with cannabis use in the general population. These include risk of addiction to other substances, diminished life achievement, increase in motor vehicle accidents, symptoms of chronic bronchitis, abnormal brain development in a younger population, psychiatric disturbances, depression, and anxiety. Studies in the general population have also shown an increased risk for cannabis hyperemesis syndrome in frequent cannabis users. Although this has not been described in the limited studies in IBD patients, I have seen it as one of the more common side effects associated with daily cannabis use in my IBD patients. Cannabis use may also have effects on fertility (both male and female), which can have implications in this often young, childbearing-age population. Overall, the small studies performed in both Crohn's disease and ulcerative colitis have failed to show serious adverse events. However, the recent study in ulcerative colitis by Irving and colleagues had significant protocol deviations, which were thought to be related to the THC content in the preparation. In addition, Naftali and colleagues' study in patients with ulcerative colitis showed an increase in memory decline in the cannabis group. These are important considerations when talking about the efficacy and tolerability of this potential adjuvant therapy.

In addition, these studies have raised some concerns about the use of cannabis specifically in the IBD population. The study by Naftali and colleagues in 30 Crohn's disease patients showed improvement in clinical symptoms; however, the majority of patients stopped conventional medical therapy. It is important to note that the studies that have been conducted have not suggested a role for cannabis as primary therapy but have studied cannabis as adjuvant therapy for patients with IBD and ongoing clinical symptoms. We know that medication noncompliance is associated with clinical relapse of disease and could have implications on disease outcomes. In addition, a large retrospective study in Canada of 300 patients with Crohn's disease found that self-reported medical cannabis use was associated with an increased risk for surgery (odds ratio, 5.30; 95% CI, 1.45-17.46). This finding comes from uncontrolled retrospective data, and it should be noted that patients using medical cannabis could have been more symptomatic, possibly due to greater disease severity, which is a known risk factor for surgery.

G&H Are there any limitations to the research that has been conducted to date?

JK Due to the federal status of cannabis as a Controlled Substance Act Schedule I drug, there have been no randomized, controlled trials evaluating the effects of cannabis in IBD patients in the United States. In addition, most of the studies in this area have looked at the administration of medical cannabis via the inhalation route, with only more recent studies looking at an oral formulation. Larger studies are needed to look at efficacy in IBD patients as well as evaluate the optimal route of administration, formulation, dosing frequency, and duration. Other limitations of the research to date include selection bias, lack of control groups, and recall bias (as patients who use cannabis and continue to use it are more likely to have subjective benefit).

> ... health care providers should know that under the federal law, they are protected from prosecution for recommending or suggesting that a patient use medical cannabis.

G&H Do you have any advice for gastroenterologists who are managing IBD patients interested in trying medical cannabis?

JK It is important for health care providers to be informed about medical cannabis, including the limited data on efficacy and adverse events, so that they can counsel their patients appropriately. Studies have shown that many patients are using cannabis, but the majority do not discuss it with their health care provider. In a recent study, up to 50% of IBD patients stated that they would use medical cannabis if it became legal, which means that many patients are coming into their health care provider's office thinking about this therapeutic approach but may not be discussing it at their office visit. Gastroenterologists should incorporate this discussion into their routine clinical evaluation of IBD patients. It is routine in my practice to ask all patients about both recreational and medical cannabis use to ensure that we can have an open

discussion about the implications of this therapy in their management strategy.

It is also important for health care providers to know that each state has its own medical cannabis laws. Although many states list Crohn's disease and/or ulcerative colitis as qualifying medical conditions, some states do not but do list symptoms associated with IBD (eg, severe pain, cachexia or wasting syndrome, severe nausea, arthritis). Most importantly, health care providers should know that under the federal law, they are protected from prosecution for recommending or suggesting that a patient use medical cannabis. Many providers are not aware of this and might avoid discussing medical cannabis because they think there may be legal or licensing implications. It is important for both patients and providers to be informed about medical cannabis to ensure its proper use and to prevent potential risks associated with the therapy. A useful guide regarding the laws associated with medical cannabis use can be found at www.safeaccessnow.org.

G&H What are the next steps in research in this area?

JK Unless there is a change in the current federal status of cannabis, we will not be able to conduct larger prospective, randomized, controlled trials in the United States to assess its effects in IBD patients. (The few randomized, controlled trials to date have been conducted in other countries.) The current US data are observational, and, although helpful to establish the potential effects, are significantly prone to bias. To better understand the therapeutic benefits of cannabis in IBD, larger prospective, controlled studies are needed. Along with several other gastroenterologists, I had the opportunity to work with the Crohn's and Colitis Foundation to release a position statement in May 2018 calling for a policy change to help facilitate further clinical research in the development of possible cannabinoid-based therapies and potentially revise cannabis' status as a Schedule I controlled substance. The full position paper will be published in *Inflammatory Bowel Diseases* by the end of 2018.

G&H Do you know of any ongoing studies in this area?

JK Naftali and colleagues are completing another randomized, controlled trial looking at moderate to severe Crohn's disease patients using CBD-THC oil for 8 weeks, and both clinical and endoscopic outcomes will be assessed. They are also looking at short- and long-term safety of medical cannabis in an IBD population. These are important studies that will help add to the current paucity of literature in this area.

Dr Kinnucan has no relevant conflicts of interest to disclose.

Suggested Reading

Irving PM, Iqbal T, Nwokolo C, et al. A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. *Inflamm Bowel Dis.* 2018;24(4):714-724.

Lahat A, Lang A, Ben-Horin S. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. *Digestion*. 2012;85(1):1-8.

Madras BK. Update of cannabis and its medical use. Presented at the World Health Organization 37th Meeting of the Expert Committee on Drug Dependence; November 16-20, 2015; Geneva, Switzerland. http://www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf. Accessed September 20, 2018.

Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol.* 2013;11(10):1276-1280.e1.

Naftali T, Bar-Lev Schleider L, Sklerovsky Benjaminov F, Lish I, Konikoff FM. Cannabis induces clinical and endoscopic improvement in moderately active ulcerative colitis. Presented at Digestive Disease Week 2018; June 2-5, 2018; Washington, DC. Abstract Sa1744.

Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. *Isr Med Assoc J.* 2011;13(8):455-458.

Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370(23):2219-2227.