

Case Report: Induction of Remission in Drug-Resistant Pediatric Inflammatory Bowel Disease with Cannabinoid Therapy

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Abstract

This case report describes a 13-year-old boy with Crohn's disease who achieved clinical and biochemical remission after oral administration of cannabinoids. After years of disease, the patient had poor appetite and suffered from weight loss and stunted growth, and failed to achieve remission with conventional therapies including the TNF- α inhibitor infliximab. The patient received three oral doses daily of 3 mg of Δ^9 -tetrahydrocannabinol (THC) and 3 mg of cannabidiol (CBD). The patient and family reported almost immediate symptomatic improvement, with increased appetite and body weight, reduced inflammatory scores, and signs of clinical remission. C-reactive protein, erythrocyte sedimentation rate, and calprotectin scores were also obtained as objective measures of disease remission following cannabinoid therapy. In particular, the calprotectin improvement suggests disease-modifying activity and not merely symptomatic relief. This clinical data suggests that cannabinoids are useful for treatment of drug-resistant pediatric inflammatory bowel disease.

Introduction

Inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis are incurable diseases of the gastrointestinal tract characterized by severe abdominal cramps, chronic diarrhea, weight loss, rectal bleeding, and pain [1]. Approximately 70% of patients with Crohn's disease and 40% of those with ulcerative colitis will require surgery at least once during the course of disease [2]. IBD is most often diagnosed in adolescence and young adulthood, with a rising incidence and prevalence in pediatric populations [3]. In children with IBD, growth deficiencies in weight and height as well as delayed puberty are recognized complications of disease activity [4].

Current therapies for IBD include aminosalicylates, corticosteroids, immune modulators, and biologics such as TNF- α inhibitors, which are directed at suppressing inflammation and preventing complications. Numerous adverse effects are associated with current IBD therapies. For instance, corticosteroids can cause mood changes, severe acne, and opportunistic infections, and long-term use can increase the risk of developing diabetes, atherosclerosis, and osteoporosis and can cause growth delay in children [5]. Biologics are the newest class of drugs used in treating IBD and include the TNF- α inhibitors infliximab and others. Blockade of TNF- α signaling can dramatically improve the course of disease for IBD patients,

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enabling steroid sparing, fewer hospitalizations and surgeries, deep remission, and better quality of life [6].

Despite the benefits of anti-TNF therapy, there are still limitations, including the failure of response in some patients, and the loss of response over time in other patients. Loss of response has been reported in 25%–40% of Crohn's disease patients in randomized controlled trials, with an estimated annual loss of response rate of approximately 13% per patient-year [7]. These findings underscore the need for new IBD therapies that can complement and/or replace existing treatments.

The endocannabinoid system (ECS) is involved in the regulation of food intake, nausea and emesis, gastric secretion and gastroprotection, gastrointestinal motility, ion transport, visceral sensation, intestinal inflammation, and cell proliferation in the gut (reviewed in [12]). Therefore, pharmacological agents that modulate the ECS are expected to have broad potential as therapeutics for treatment of gastrointestinal conditions including IBD. Indeed, beneficial effects of cannabinoids in the gastrointestinal tract have been recognized for centuries, and animal models of colitis have suggested that some of these effects may occur through targeting of inflammatory mediators [8-11]. Many of the biological effects of cannabinoids are mediated by cannabinoid receptors 1 (CB1) and 2 (CB2), which are found throughout the gastrointestinal tract. The plant *Cannabis sativa* is the source of multiple cannabinoids that act on these receptors, including Δ^9 -tetrahydrocannabinol (THC), the main psychoactive compound, and cannabidiol (CBD), which does not have intoxicating psychoactive effects.

Patients with IBD report that use of cannabis can improve appetite, nausea, abdominal pain, abdominal cramping, joint pain, and diarrhea [12-14]. Both retrospective and prospective clinical trials in IBD patients have shown that use of cannabis is associated with substantial symptomatic relief, and placebo-controlled trials have confirmed significant declines in disease activity scores [12-17]. However, these trials largely relied on subjective outcome measures.

In formal clinical trials, objective diagnostic measures are preferred to reduce introduction of bias when measuring treatment outcomes, and for IBD many objective diagnostic measures already exist, including calprotectin and C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). The fecal calprotectin level has emerged [18] as a particularly useful and reliable measure of active bowel disease in pediatric populations, as it is non-invasive, objective, and also specific measure of local intestinal inflammation, rather than a broad measure of systemic inflammation such as CRP. In fecal calprotectin assays, quantification of leakage or active release of calprotectin into the stool from the inflamed intestinal lining provides an objective index for IBD severity. It has been found that calprotectin scores correlate well with healing of the gut mucosal lining based on endoscopically identified lesions in both Crohn's disease and ulcerative colitis [19, 20]. CRP is a systemic (blood) marker used to diagnose and predict the activity of inflammatory disease. CRP is produced predominantly in the liver in response to

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acute stimulation by interleukin (IL)-6, TNF- α , and IL-1 β produced at the site of inflammation [21]. The CRP level that defines systemic inflammation is 0.8 mg/dL (8 mg/L), and once the acute phase of inflammation disappears, CRP levels quickly decrease because of its relatively short half-life. The ESR is a non-specific marker of inflammation that is not immediately responsive to change in clinical status; however, it is highly correlated with IBD disease activity. Therefore, it is an important measure of colonic disease, including ulcerative colitis and Crohn's disease within the large bowel [22].

We herein describe a case study involving a drug-resistant pediatric IBD patient who achieved clinical remission following treatment with cannabinoid therapy, as determined using CRP and fecal calprotectin levels as well as the ESR. This is the first case, to our knowledge, with reporting of fecal calprotectin levels and ESR as objective measures of clinical response.

This single case study is exempt from Institutional Review Board approval. All medical information was submitted voluntarily by the patient's family and written consent was obtained to authorize its publication.

Case Report

The patient was diagnosed with Crohn's disease in February 2013 at age 9, and is currently 13 years old. The formal diagnosis by the patient's gastroenterologist was Crohn's disease with mild-to-moderate distal colitis and aphthous ileal ulcerations. The patient was hospitalized several times throughout the course of the disease and put on steroids and a morphine drip. He was treated with the TNF- α inhibitor infliximab for more than one year at 5-week intervals, but conventional therapies including infliximab failed to induce remission. Medications that were tried without success include sulfasalazine, Lialda™(mesalamine), CANASA® (mesalamine rectal suppository), and azathioprine. Methotrexate was tried and caused severe side effects. After confirmation of active disease based on a calprotectin level higher than 400 $\mu\text{g/g}$ in late 2015, use of infliximab was continued as the primary method of treatment. Temporary symptomatic benefit was observed but quickly dissipated, and the calprotectin level then increased to higher than 2,000 $\mu\text{g/g}$ during the following four months of infliximab treatment.

After years of disease that could not be controlled with conventional therapies, the patient continued to suffer from poor appetite, weight loss, anemia, and stunted growth. Because of Crohn's disease symptoms or hospitalization, he missed approximately 25 days per school year. He also had intense stomach cramps, anemia, and bloody diarrhea 10-20 times per day. The patient had suffered from five consecutive infections with *Clostridium difficile*, for which he had been hospitalized. Available antibacterial medications including vancomycin were ineffective; therefore, the patient's family arranged for treatment with fecal transplants through a specialist, which resolved the infection and achieved temporary remission of IBD.

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The patient's family learned of the success of Coltyn Turner, a well-known Crohn's disease patient who reported clinical remission of drug-resistant Crohn's disease using cannabis [17] after failure of conventional therapies while being treated at the Mayo Clinic. The patient's family received approval for treatment with cannabis under the California Compassionate Use Act. In mid-February 2016, the patient began cannabinoid therapy with chocolate bars that were each infused with 3 mg of Δ^9 -tetrahydrocannabinol (THC) and 3 mg of cannabidiol (CBD), receiving 3 doses per day. The patient and family reported almost immediate symptomatic improvement, with increased appetite and body weight, reduced inflammatory scores, and induction of remission.

By one month, the patient had achieved remission, as determined by calprotectin scores decreasing from over 2000 $\mu\text{g/g}$ to 86 $\mu\text{g/g}$ (Figure 1). Serum levels of CRP were 13-18.5 mg/L from Dec 1, 2016 to March 1, 2016, and decreased to 0 mg/L on April 1, 2016, two months after initiation of cannabinoid therapy in mid-February 2016 (Figure 2). Similarly, the serum erythrocyte sedimentation rate was reduced from 25 mm/hr to 3 mm/hr (Figure 3).

The time between infliximab infusions was extended from 5 weeks to 9 weeks against the advice of the attending gastroenterologist. The patient appeared to be in remission and did not appear to require additional therapeutics; therefore, the family stopped infliximab treatments on January 3, 2017. The patient is currently in complete remission with no Crohn's disease symptoms, and has been in clinical remission for more than a year since initiation of cannabinoid therapy. The patient has continued to increase height and gain body weight since starting cannabinoid therapy (Figure 4). The patient's school attendance has improved, and he has not missed any days of school due to hospitalization. No adverse reactions to cannabinoid therapy were reported.

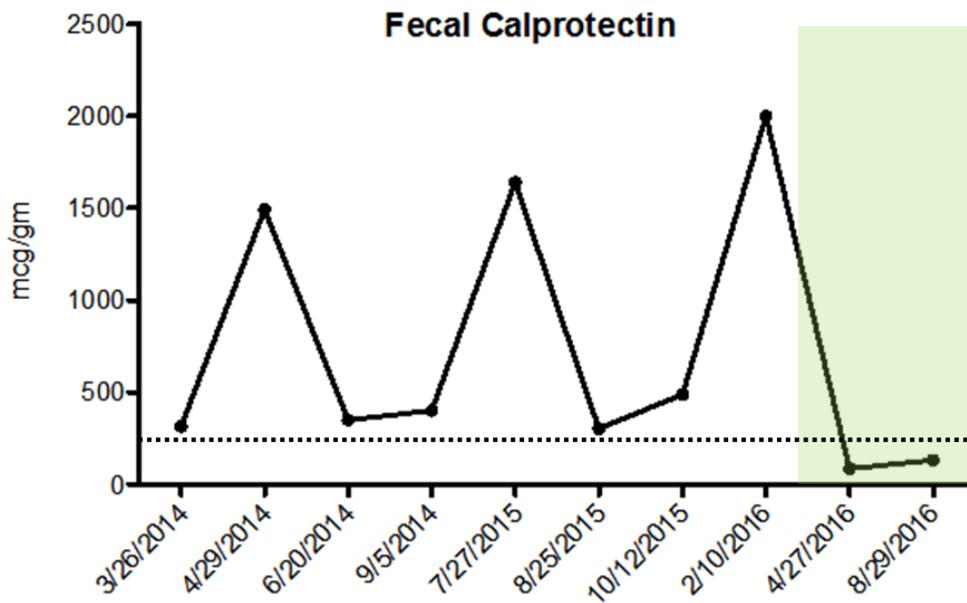


Figure 1. Fecal Calprotectin Levels

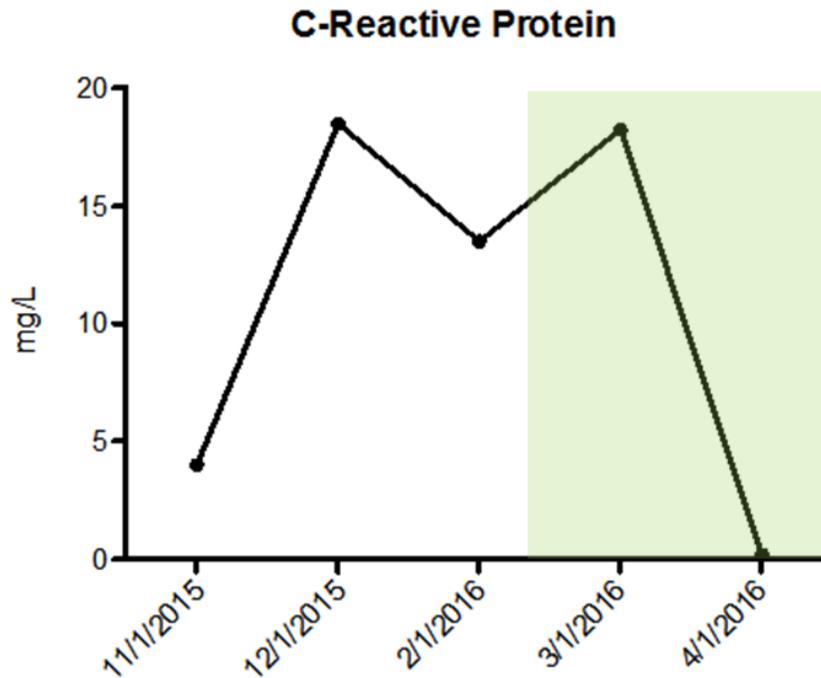


Figure 2. C-Reactive Protein Levels

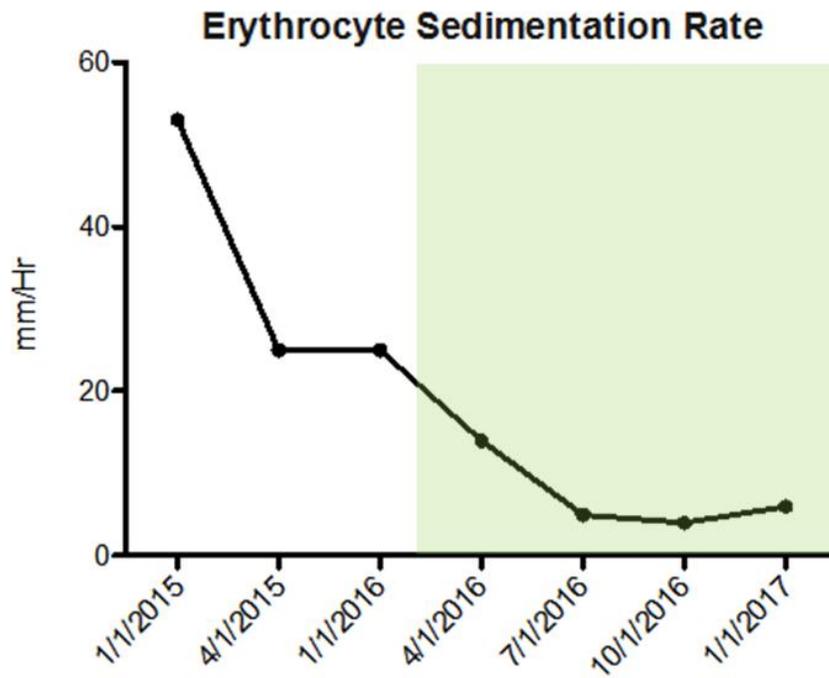


Figure 3. Erythrocyte Sedimentation Rate

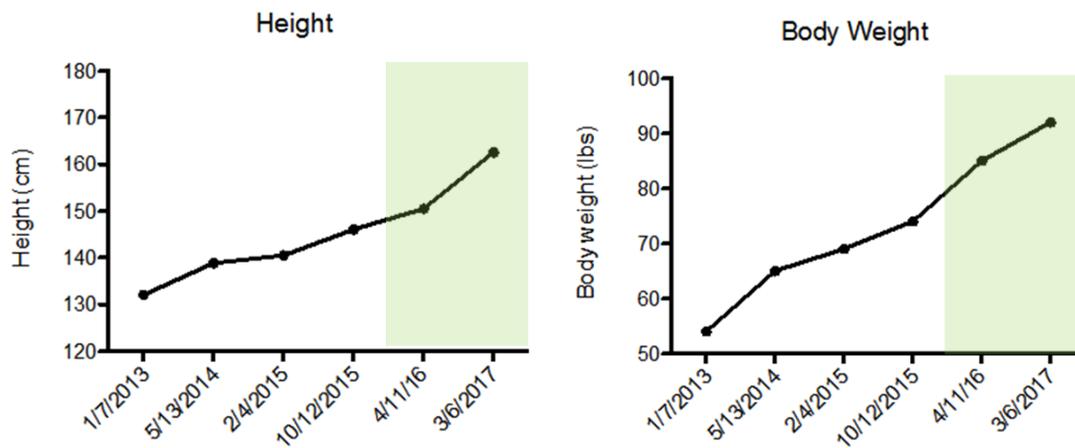


Figure 4. Height and Body Weight

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Discussion

This is the first report of cannabinoid therapy inducing remission in a pediatric IBD patient; furthermore, the outcome was determined using objective measures of disease activity.

Both retrospective [12, 23] and prospective studies [15, 16] have assessed the use of cannabis for inflammatory bowel disease, with significant improvements in the quality of life for IBD patients. The first prospective study, reported by Lahat and colleagues, included 13 patients with longstanding IBD that was resistant to treatment with conventional therapies. The patients used inhaled cannabis, dosed ad libitum for pain, and the average Harvey-Bradshaw disease activity index was reduced from 11.36 to 2.68 ($p=0.001$); improvements were predominantly seen in patients' general well-being and relief of abdominal pain. Naftali and colleagues completed the first placebo-controlled, prospective study and evaluated 21 Crohn's disease patients who had failed conventional therapies, including corticosteroids, immunomodulators, biologic agents such as TNF-alpha inhibitors, and aminosalicylates. The patients were on stable medications prior to initiating treatment for 8 weeks with inhaled cannabis (230 mg of THC daily), and disease activity was measured using the Crohn's Disease Activity Index (CDAI). All patients had CDAI scores higher than 200 upon initiation of the trial. Of those treated, 5 of 11 (45%) entered into a clinical definition of remission within 8 weeks, compared to only 1 of 10 controls. With 8 weeks of treatment, 10 of 11 in the treatment group had CDAI reductions greater than 100 points, from an average score of 330 to 152, compared to the placebo group who had an average reduction from 373 to 306 ($p=0.028$). Naftali and colleagues also reported that 3 patients who were previously corticosteroid-dependent were able to stop corticosteroid use, and that none of the patients in the treatment group required corticosteroids at the end of the study. In the treatment group, 2 patients who had been using opiates for chronic pain were able to halt opiate use during the study. Given the inability to treat these patients with conventional therapies, the clinical results appear impressive; however, additional data are required to further validate the role of cannabinoid drugs for treatment of IBD.

One shortcoming of studies evaluating cannabinoid therapy for IBD, however, is their reliance on subjective measures reported by patients, which makes it difficult to standardize results, to identify the mechanisms of action for the treatment, and to determine whether the therapy is actually disease-modifying or only useful for controlling symptoms. Regarding objective measures, studies to date have not included endoscopic findings, and anti-inflammatory effects have only been measured using a single marker, CRP, which assesses systemic inflammation.

In summary, we have described a case study of a patient with drug-resistant pediatric IBD who achieved clinical remission following cannabinoid therapy. This is the first case, to our knowledge, to monitor fecal calprotectin levels, which have emerged as a reliable measure of active disease in pediatric IBD populations. In

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particular, fecal calprotectin levels correlate well with the presence of endoscopic lesions, and decreased levels correlate well with healing of the gut mucosal lining in both Crohn's disease and ulcerative colitis. Based on these findings, we expect that treatment of local gut inflammation with cannabinoids may not only resolve symptoms of IBD but also achieve disease modification by inducing and maintaining remission.

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