A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis

Peter M Irving, MA MD FRCP[1,], Tariq Iqbal, MD FRCP[†], Chuka Nwokolo, MD FRCP[‡], Sreedhar Subramanian, MD MRCP[§], Stuart Bloom, FRCS MRCP DM[¶], Neeraj Prasad, MRCP MSc[‖], Ailsa Hart, MRCP PhD[**], Charles Murray, MA PhD FRCP[††], James O. Lindsay, MA PhD FRCP[‡‡], Adam Taylor, PhD[§§], Rachel Barron, BVetMed MRCVS[§§], and Stephen Wright, MA MD FRCPE FFPM[§§]*

Background: Cannabidiol (CBD) exhibits anti-inflammatory properties that could improve disease activity in inflammatory bowel disease. This proof-of-concept study assessed efficacy, safety and tolerability of CBD-rich botanical extract in ulcerative colitis (UC) patients.

Methods: Patients aged 18 years or older, with left-sided or extensive UC, Mayo scores of 4–10 (endoscopy scores ≥1), and on stable 5-aminosalicylic acid dosing, were randomized to 10-weeks' CBD-rich botanical extract or placebo capsules. The primary endpoint was the percentage of patients in remission after treatment. Statistical testing was 2-sided, using a 10% significance level.

Results: Patients were less tolerant of CBD-rich botanical extract compared with placebo, taking on average one-third fewer capsules, and having more compliance-related protocol deviations (principally insufficient exposure), prompting identification of a per protocol (PP) analysis set. The primary endpoint was negative; end of treatment remission rates were similar for CBD-rich botanical extract (28%) and placebo (26%). However, PP analysis of total and partial Mayo scores favoured CBD-rich botanical extract ($P = 0.068$ and $P = 0.038$, respectively). Additionally, PP analyses of the more subjective physician's global assessment of illness severity, subject global impression of change, and patient-reported quality-of-life outcomes were improved for patients taking CBD-rich botanical extract ($P = 0.069$, $P = 0.003$, and $P = 0.065$, respectively). Adverse events (AEs) were predominantly mild/moderate with many in the CBD-rich botanical extract group potentially attributable to the Δ^9-tetrahydrocannabinol content. A greater proportion of gastrointestinal-related AEs, indicative of UC worsening, was seen on placebo.

Conclusion: Although the primary endpoint was not reached, several signals suggest CBD-rich botanical extract may be beneficial for symptomatic treatment of UC.

Key Words: Cannabidiol, cannabinoid, inflammatory bowel disease, ulcerative colitis, Mayo

INTRODUCTION

Ulcerative colitis (UC) affects approximately 240 people per 100,000 adults[1] and is a chronic, relapsing, and remitting inflammatory bowel disease (IBD). Active disease usually causes rectal bleeding and diarrhea and will often also result in pain, fatigue, and weight loss. Patients with chronic intestinal inflammation also have an increased risk of developing bowel cancer.[2]

First line therapy for mild to moderate UC is 5-aminosalicylic acid (5-ASA), which is effective at inducing and maintaining remission in approximately 50% of patients.[3] The majority of patients with moderate to severe active UC require topical, oral, or parenteral glucocorticosteroids, and azathioprine or 6-mercaptopurine have been employed as glucocorticoid-sparing agents in steroid-dependent patients.[4] In 2006, the first anti-tumour necrosis factor (TNF) agent was approved for the treatment of UC, followed more recently by

Received for publications 8 February 2017; Editorial Decision 15 December 2017

From the *Guy's and St Thomas' NHS Foundation Trust, London, UK; †University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; ‡University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; §The Royal Liverpool and Broadgreen University Hospitals NHS Foundation Trust, Liverpool, UK; ¶University College Hospitals NHS Foundation Trust, London, UK; ‖Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK; **The North West London Hospitals NHS Foundation Trust, Middlesex, UK; ††Royal Free London NHS Foundation Trust, London, UK; ‡‡The Royal London Hospital, Barts Health NHS Trust, London, UK; §§GW Research Ltd, Cambridge, UK.

Conflicts of Interest: P. Irving, T. Iqbal, C. Nwokolo, S. Subramanian, S. Bloom, N. Prasad, A. Hart, and C. Murray were all investigators in the study and received investigator fees from GW accordingly for their participation.

GW medical writers R. Barron and A. Taylor undertook the initial compilation and quality control review of the manuscript; both are employed by, and hold shares in, GW.

S. Wright is employed by and holds shares in GW.

Supported by: The study was sponsored by GW Research Ltd (GW). GW was involved in the study design, data collection, and analysis, as well as in the preparation of this manuscript and publication decisions.

[1]Address correspondence to: Dr Peter Irving, MA MD FRCP, Department of Gastroenterology, First Floor College House, North Wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH, United Kingdom. E-mail: peter.irving@gstt.nhs.uk.

doi: 10.1093/ibd/izy002
Published online 10 March 2018

the anti-integrin therapy vedolizumab.[5,6] The calcineurin inhibitors cyclosporin and tacrolimus also have limited but established roles to play.[7] However, a proportion of patients have mild to moderate UC that is resistant to current standard therapies and require alternative treatment.[8]

Cannabis sativa L. plants produce trichomes that exude a resin containing a specific mix of cannabinoids,[9,10] of which the 2 principal components are Δ^9-tetrahydrocannbinol (THC) and cannabidiol (CBD). GW Research Ltd. (GW) (Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, CB24 9BZ) produces plants with defined chemical profiles (chemotypes), including one that contains predominantly CBD.[10] The CBD-rich botanical extract from the CBD chemotype contains CBD and smaller amounts of other compounds such as cannabigerol, terpenoids, flavonoids, sterols and 3.2%–4.7% THC.

Cannabinoid administration is associated with a number of beneficial effects in the gut including decreasing emesis, gastric acid secretion, inflammation and intestinal motility.[11,12] Cannabis has been reported to produce symptom improvement in people with IBD[13] and some patients self-medicate with cannabis.[13]

CBD, a major component of cannabis with low abuse potential,[14] has been shown to have anti-inflammatory and immune modulating properties.[15] Preclinical models of IBD have suggested that CBD may have utility in the treatment of UC. Although the mechanism of action is not fully understood, it has been shown to exert beneficial effects in the inflamed gut, including a reduction in intestinal inflammation and inhibition of inflammatory hypermotility, and has been shown to prevent experimental colitis in mice.[16,17]

In addition, CBD-rich botanical extract contains an appreciable amount of THC, which is a partial agonist at 2 endogenous cannabinoid receptors.[18] As part of the endocannabinoid system (ECS), these CB_1 and CB_2 receptors are involved in physiological and pathophysiological actions in the gastrointestinal tract (e.g., peristalsis, secretion, gastric emptying, emesis, satiety, immunomodulation/inflammation and pain).[19–21]

There is evidence that the combination of CBD and THC may offer additive effects in models of inflammatory bowel disease. Jamontt et al. (2010) reported on the effects of THC and CBD, alone and in combination, compared with a positive control, sulphasalazine, on damage, inflammation and *in vitro* motility disturbances in rat colitis.[22] In this study, THC and CBD at optimal doses of 10 mg/kg, not only reduced inflammation but also lowered the occurrence of functional disturbances.[22]

We therefore investigated the efficacy and safety of the investigational medicinal product, CBD-rich botanical extract treatment, in patients with mild to moderate UC which had proved refractory to 5-ASA therapy.

MATERIALS AND METHODS

Study design

This 12-week (1-week baseline, 10-week treatment period, 1-week follow-up), multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of CBD-rich botanical extract compared with placebo in patients with mild to moderate UC which had proved refractory to 5-ASA. It was conducted in 9 centers in the United Kingdom. The study protocol and results are registered on the clinicaltrials.gov website (NCT01562314).

Inclusion and exclusion criteria

To be eligible, patients were previously diagnosed with mild to moderate UC with screening and baseline Mayo assessment scores of ≥4 but ≤10 and an endoscopy subscore of ≥1. Those with severe UC (Mayo score >10) or stand-alone proctitis were not eligible. Patients were also required to be on a stable dose of 5-ASA treatment during the study and for at least 2 weeks prior to screening, although taking no 5-ASA was permissible if they had previously tried and failed the treatment.

Patients with evidence of a gastrointestinal infection on stool culture and testing for *Clostridium difficile* toxin and those who had previously not responded to anti-TNF antibodies were not eligible. Likewise, patients who had received any prohibited medications prior to screening or during the study (systemic steroids in the past 4 weeks, topical UC treatments in the past 2 weeks, or immunomodulating drugs in the past 3 months prior to study entry [other than stable doses of azathioprine, mercaptopurine, or methotrexate]) were excluded. Those who were using or had used cannabis (recreational or medicinal) in the month prior to study entry, and were unwilling to abstain for the duration of the study, and those who had received another investigational medicinal product within 30 days of the screening visit were not included. Patients with any known or suspected history of alcohol or substance abuse or any current or past history of significant psychiatric illness, other than reactive depression, were also excluded. Finally, any patients with concomitant disorders or abnormalities that could either put them at risk, affect their ability to participate, or influence the results of the study were ineligible. This included patients who were hypersensitive to cannabinoids; patients with epilepsy or recurrent seizures; female patients who were pregnant, lactating, or planning pregnancy; and patients with plans to travel outside of the country during the treatment phase of the study.

Study medication and procedures

Following eligibility screening, patients were randomly assigned CBD-rich botanical extract or placebo (1:1), and baseline assessments were performed. Study medication was presented as hard gelatin capsules containing 50 mg CBD-rich

botanical extract in excipients or matching placebo capsules containing excipients only. These were taken twice daily by mouth, 30 minutes before morning and evening meals. Following randomization, patients entered a 2-week dose escalation period during which they were required to reach their maximum tolerated dose of up to 250 mg (5 capsules) twice daily. Patients were then requested to maintain this dose for the remaining 8 weeks of the treatment period. On-treatment visits occurred at the end of week 2 and week 6 (visit 3 and visit 4) and at end of treatment (week 10, visit 5), or earlier in the case of withdrawal. A safety follow-up visit occurred at least 7 days after the end of treatment or withdrawal.

Throughout the study, any concomitant medications deemed necessary to provide adequate supportive care could be prescribed, except for those listed in the exclusion criteria or those that could potentially affect the primary or other efficacy endpoints.

Study endpoints

The primary endpoint was the percentage of patients in remission at the end of treatment, quantified as a Mayo score of ≤2 (with no subscore >1), after 10 weeks' treatment.

The secondary endpoints were the change from baseline to end of treatment in the following: inflammatory marker levels (blood C-reactive protein [CRP], plasma interleukin [IL]-2, IL-6, TNF-α, and faecal calprotectin); inflammatory bowel disease questionnaire (IBDQ) score; physician global assessment of illness severity (PGAS) score; stool frequency and rectal bleeding on 4-point numerical rating scales (NRS); pain 0–10 NRS score; Mayo score (total and a 9-point partial score that summed rectal bleeding, stool frequency, and PGAS scores, to compensate for patients without end of study endoscopies); responders (defined as a decrease in their Mayo score of ≥3 compared with baseline and a reduction of at least 1 in endoscopic subscore); subject global impression of change (SGIC); and body weight.

The safety endpoint was assessment of the safety and tolerability of CBD-rich botanical extract compared with placebo through adverse events (AEs) and changes in vital signs, electrocardiogram (ECG), and laboratory and physical parameters.

Sample size

Based on the assumption of a 20% remission rate with placebo and a 50% remission rate with CBD-rich botanical extract, 62 patients (randomized 1:1 to either CBD-rich botanical extract or placebo) were required to detect this difference at the 10% level of significance (2-tailed) with 80% power.

Methods of assigning patients to treatment groups and blinding

An independent statistician produced a randomization schedule which was held centrally. Patients were each allocated a unique number and were then assigned to either the CBD-rich botanical extract or placebo treatment arm according to the randomization schedule. The process used enabled allocation to be concealed.

To maintain blinding throughout, all capsule medication was formulated to disguise the appearance, smell, and taste of the active CBD-rich botanical extract by using identical excipients and capsule shells. The maximum number of dose units administered was identical in both treatment groups.

Statistical methods

The primary analyses used the intention to treat (ITT) analysis set (comprising all patients who were randomized and received at least 1 dose of study medication).

Major protocol deviations (i.e., those deemed likely to compromise the assessments of efficacy) were identified during blinded review of the data and consisted of patients with insufficient exposure to the study medication (<28 days treatment) or who had had more than a 7-day gap between their last dose of study medication and their final study visit. Due to the high number of patients in the CBD-rich botanical extract group falling into 1 of these categories, the per protocol (PP) analysis set (comprising all patients with no major protocol deviations) differed substantially from the ITT analysis set, so further analyses using the PP analysis set were also performed.

Statistical hypothesis testing was performed on the primary endpoint and other endpoints as appropriate. As this was a proof-of-concept study, no formal adjustment of statistical significance for multiple testing was done, although multiplicity should be allowed for when interpreting results. All statistical tests were 2-sided and, due to the unknown impact of CBD-rich botanical extract on the planned outcome measures, the 10% significance level was pre-specified, as is often the practice in early, exploratory studies.

For the primary endpoint, the proportion of patients in remission was analyzed using a logistic regression model with response status (remission/non-remission) modeled by including treatment group as factor and baseline Mayo score as covariate.

The secondary endpoints, SGIC, and Mayo responders were also analysed using logistic regression. For all other secondary endpoints, changes from baseline score to end of treatment score were analyzed using an analysis of covariance (ANCOVA) model, with baseline score/value as covariate and treatment and gender as factors. From this analysis, the adjusted treatment means, treatment difference, standard error, p-value, and 90% confidence interval (CI) for the treatment difference were presented.

The possibility of an interaction between treatment and center was investigated during the analysis process through inclusion of a center effect (with no grouping) in the statistical model. Other key baseline characteristics were also included in

the model on an exploratory basis to see whether they had any impact on the efficacy results.

ETHICAL CONSIDERATIONS

The study was approved by the Leicester Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki and the ICH GCP guidelines. All patients were aged 18 years old or older and provided written informed consent before any study related procedures were carried out. The trial lasted approximately 2 years; the first patient was screened on May 9, 2012, and the last patient's last visit was August 5, 2014.

RESULTS

A total of 75 patients were screened over a 24-month period, and 60 were randomized; 29 were assigned to CBD-rich botanical extract and 31 to placebo; 39 patients completed the study. These patients were recruited at 9 separate UK centers, with 8 of these centers randomizing a median of 5.5 patients each (range 2–17) into the ITT population, and a median of 5 patients each (range 1–12) into the PP population. The intended 62 randomized patients were not achieved due to a very slow recruitment rate. A total of 21 patients withdrew, 15 of whom withdrew due to AEs: 10 in the CBD-rich botanical extract group, compared with 5 in the placebo group. A further 5 patients were withdrawn because they met 1 or more of the withdrawal criteria which, in all cases, were also associated with AEs. One patient withdrew consent (Fig. 1).

The demographic profiles of patients in both treatment groups were similar, with the majority of patients being white/caucasian and male (Table 1). Although the majority of patients were cannabis-naive, a higher proportion of those randomized to the CBD-rich botanical extract group had previously used cannabis, compared with the placebo group (ITT analysis set: 9 [31%] patients versus 4 [13%], respectively). Though on average, time since last use was greater (13.8 years for the CBD-rich botanical extract group versus 10.0 years for placebo); differences between the 2 treatment groups in the PP analysis set were less marked (Table 1).

Medications being taken concomitantly for UC were largely similar between the active and placebo treatment groups in both the ITT and PP analysis sets (Table 1). For patients taking 5-ASA, the majority in both treatment groups were taking pH-dependent preparations.

Disease duration was similar in the 2 treatment groups (ITT analysis: mean 9.8 years in the CBD-rich botanical extract group, compared with 8.7 years for the placebo group), as was the time since the last change in 5-ASA dose. Mean Mayo score

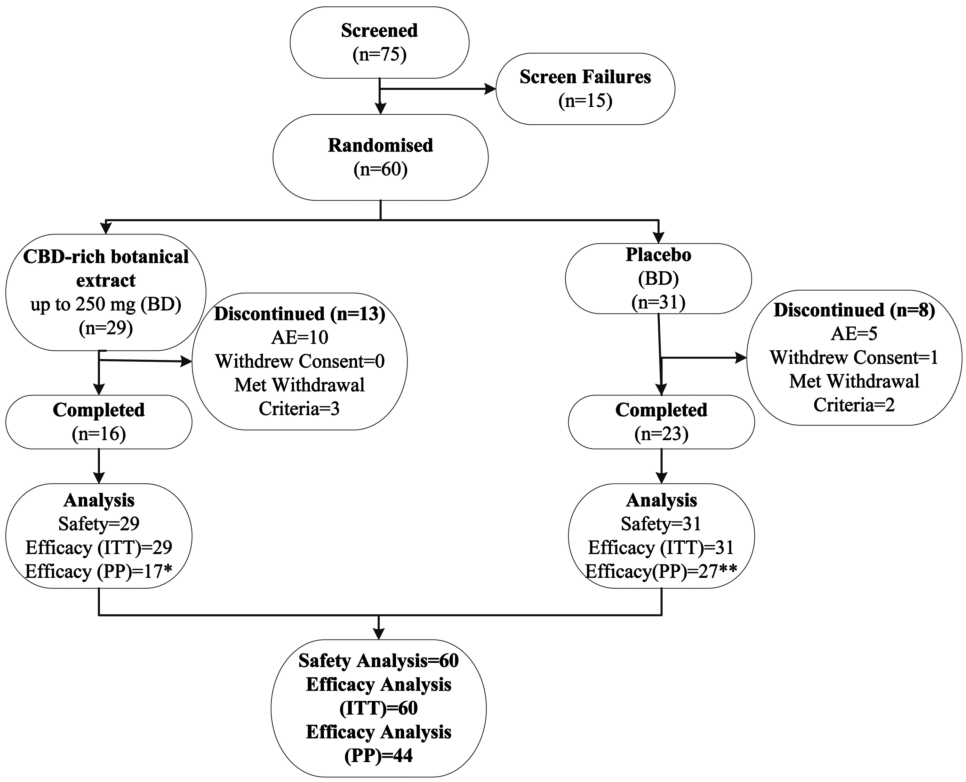

Figure 1. CONSORT flow diagram of patient disposition. *In the CBD-rich botanical extract group, the PP population excluded 7 patients with insufficient exposure to study medication (28 days or less), 2 patients who took their final dose of study medication ≥7 days before the final assessments visit, and 3 patients who met both of these criteria. **In the placebo group, the PP population excluded 3 patients with insufficient exposure to study medication (28 days or less), and 1 patient who took their final dose of study medication ≥7 days before the final assessments visit.

TABLE 1: Demographics and Baseline Characteristics Including Concomitant Medications Taken for Ulcerative Colitis in >1 Patient

		Number (%) of Patients			
		ITT Analysis Set		PP Analysis Set	
		CBD-rich Botanical Extract (n = 29)	Placebo (n = 31)	CBD-rich Botanical Extract (n = 17)	Placebo (n = 27)
Gender	**Male**	23 (79)	21 (68)	15 (88)	20 (74)
	Female	6 (21)	10 (32)	2 (12)	7 (26)
Ethnic Origin	**White/Caucasian**	21 (72)	22 (71)	12 (71)	20 (74)
	Black/African American	1 (3)	0	1 (6)	0
	Asian	6 (21)	6 (19)	3 (18)	5 (19)
	Other	1 (3)	3 (10)	1 (6)	2 (7)
Previous Cannabis Use		9 (31)	4 (13)	5 (29)	4 (15)
No. patients taking concomitant UC medications:		25 (86)	26 (84)	15 (88)	24 (89)
Mesalazine		23 (79)	23 (74)	14 (82)	21 (78)
Azathioprine		4 (14)	5 (16)	1 (6)	5 (19)
Mercaptopurine		3 (10)	3 (10)	3 (18)	4 (15)
Balsalazide		1 (3)	3 (10)	1 (6)	2 (7)
VSL 3		0	2 (6)	0	2 (7)
		Mean (SD)			
Age (years)		44.8 (15.1)	42.8 (12.9)	43.2 (14.2)	43.4 (13.3)
BMI (kg/m^2)		27.3 (5.8)	26.0 (5.2)	28.5 (6.2)	26.7 (5.2)
Time Since Last Cannabis Use (years)		13.8 (10.7)	10.0 (11.3)	7.1 (4.7)	10.0 (11.23)
Disease Duration (years)		9.8 (10.7)	8.7 (7.6)	8.7 (9.4)	9.6 (7.8)
Mayo Score at Screening		6.9 (1.6)	7.4 (2.0)	6.9 (1.7)	7.4 (2.1)
Time Since Last Change in 5-ASA Dose (years)		1.6 (2.7)	1.1 (1.7)	1.3 (2.6)	1.3 (1.8)
Time Since Last Use of Topical Treatment (years)		2.2 (5.6)	0.4 (0.6)	3.2 (7.4)	0.5(0.6)

at screening was 6.9 points for the CBD-rich botanical extract group and 7.4 points for the placebo group; the difference was not statistically significant, and both groups included patients at the top (10 points) and bottom (4 points) of the accepted range for entry into the study. In all cases, the PP analysis set had very similar disease characteristics to the ITT analysis set.

The only notable difference in baseline data between the 2 treatment groups was in the time since last use of topical treatment, which was more than 2 years ago in the CBD-rich botanical extract group compared with less than 6 months ago in the placebo group (ITT analysis set) and was even more marked in the PP population.

Patients randomized to CBD-rich botanical extract were less adherent, as demonstrated by a disproportionate number of early withdrawals and lower daily dosing levels. Although dosing started at a similar level for both groups, it diverged during the dose escalation period, and throughout the maintenance period patients in the CBD-rich botanical extract group were taking, on average, one-third fewer capsules than those on placebo (Fig. 2). Mean duration of exposure was also shorter in the CBD-rich botanical extract group (48 days compared with 61 days for placebo). There were more compliance-related major protocol deviations in the CBD-rich botanical extract group (CBD-rich botanical extract, 12 [41%] patients versus placebo, 4 [13%] patients), principally insufficient exposure, culminating in the PP analysis set of 17 CBD-rich botanical extract patients compared with 27 patients in the placebo group. With only 59% protocol compliance in the CBD-rich botanical extract ITT set, many analyses were also conducted on the PP analysis set. While it was possible that with more patients being excluded from the active than the placebo group, the PP analysis set might have been affected by selection bias, it was deemed important to look at the subset of patients whose treatment compliance was sufficient to have an effect, and so the PP analysis was considered relevant for assessing efficacy.

Primary endpoint

The primary endpoint was negative. For the ITT analysis set, remission was seen in both groups at end of treatment at approximately equal levels (odds ratio [OR] = 0.82; 90% CI:

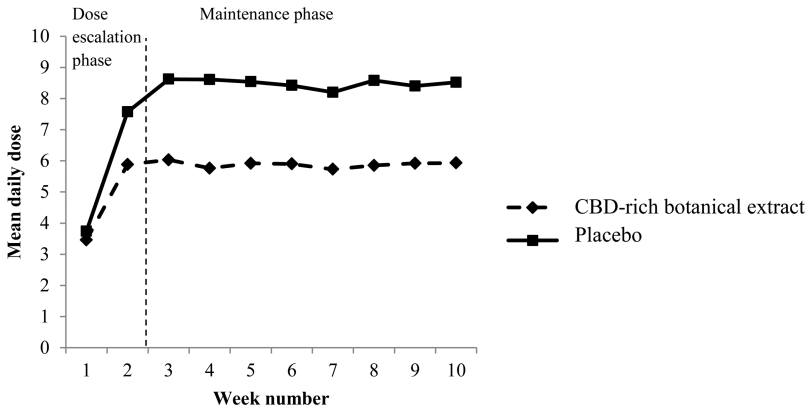

FIGURE 2. Mean daily dose (number of capsules) of study medication by week.

0.29–2.31; P = 0.753). Using the PP analysis set, there was a greater percentage of patients in remission in the CBD-rich botanical extract group: 7 (41%) patients, compared with 8 (30%) placebo patients, although the difference was not statistically significant (OR = 1.30; 90% CI: 0.42–4.04; P = 0.703).

Secondary endpoints

Prior to dosing, no patients had a PGAS severity score rated as "normal," and approximately 75% of all scores were rated as either "moderate" or "severe," with little variation between the 2 treatment groups. Improvements were observed in the CBD-rich botanical extract group by the end of treatment, at which point 77% of assessments classed disease severity as "normal" or "mild," compared with 52% in the placebo group (treatment difference −0.34; 90% CI: −0.72 to 0.03; P = 0.132). In the PP analysis set; 82% of patients were classified as having mild to normal disease severity by the end of treatment in the CBD-rich botanical extract group, compared with 52% in the placebo group (treatment difference = −0.50; 90% CI: −0.95 to −0.05; P = 0.069).

The patient-reported quality of life, as measured using the IBDQ and SGIC assessments, were consistent with the physicians' views. Results from the IBDQ (total score and the 4 domains of bowel symptoms, systemic symptoms, emotional status, and social functioning) increased in both treatment groups (Fig. 3). Increases were greater in the CBD-rich botanical extract group for all but the systemic symptoms domain, and overall, though the ITT analysis of the change in total IBDQ score did not reach statistical significance, the PP analysis did; treatment difference 25.3; 90% CI: 2.86–47.65; P = 0.065. For the SGIC, a higher proportion of patients reported feeling better by the end of treatment, which was significantly in favor of CBD-rich botanical extract for both the ITT and PP analysis sets (Fig. 4).

Stool frequency and rectal bleeding scores were similar in both groups at baseline, and improvements in both were seen across the course of the study in both treatment groups. In the CBD-rich botanical extract treatment group, 14 out of 21 (66.7%) patients showed an improvement in their endoscopic subscore compared with 10 out of 26 (38.5%) patients on placebo (P = 0.054). Although rectal bleeding subscores were

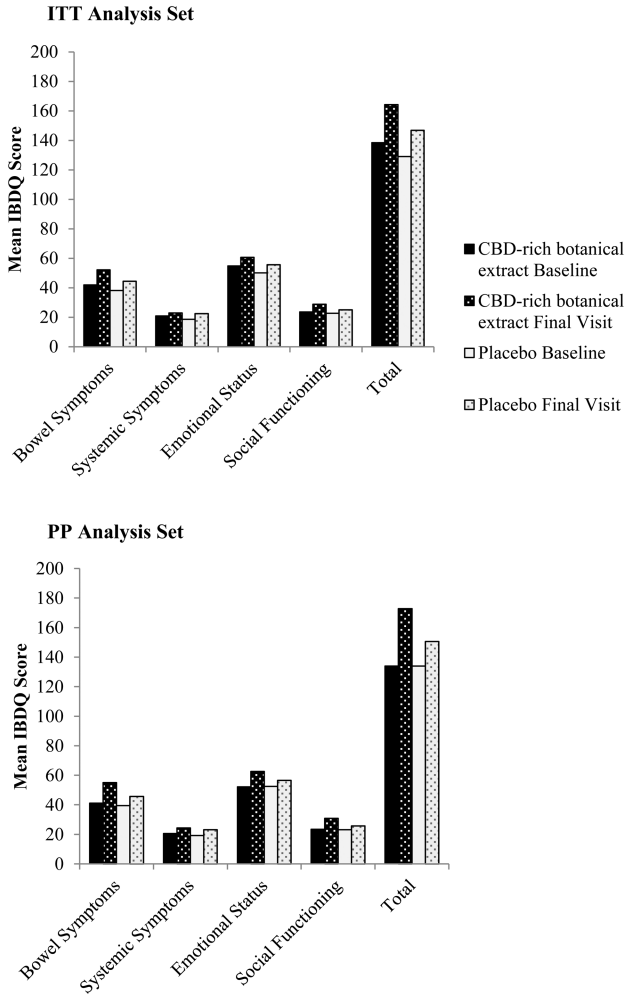

FIGURE 3. Mean baseline and end of treatment IBDQ scores—ITT and PP analyses.

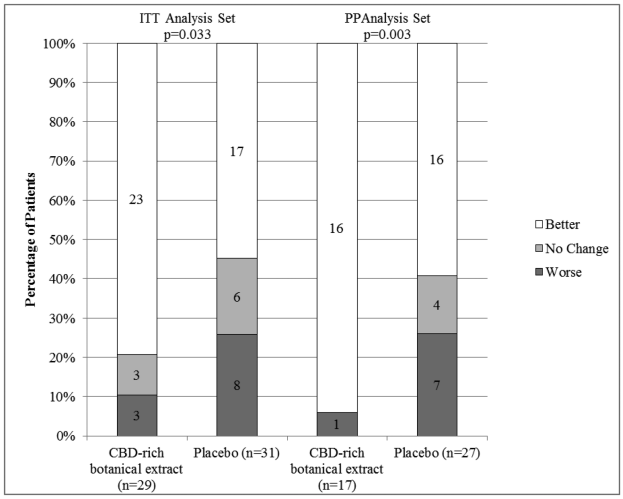

FIGURE 4. Analysis of subject global impression of change at visit 5—ITT and PP analyses.

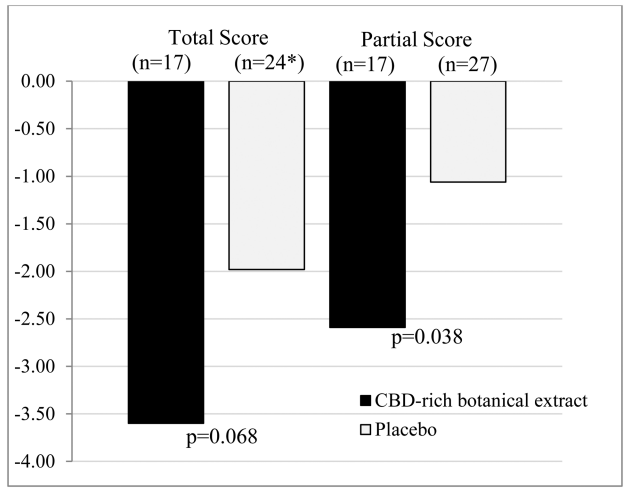

FIGURE 5. Mayo total and partial scores: change from baseline to final visit—PP analysis set.*In the placebo group, only 24 patients have a total Mayo score as 3 did not have an end of treatment endoscopy performed.

lower at the end of treatment, (−0.64 in the CBD-rich botanical extract groups versus −0.30 in the placebo group for the PP analysis set), this was not statistically significant.

Mean Mayo total scores for both treatment groups were comparable at screening and baseline, and a reduction in Mayo total score was observed in both groups. Although this was more pronounced in the CBD-rich botanical extract group for the ITT analysis set, it was not statistically significant (treatment difference = −1.23; 90% CI: −2.60 to 0.14; $P = 0.138$). However, the PP analysis of the change in Mayo total score from baseline did significantly favor CBD-rich botanical extract (treatment difference = −1.61; 90% CI: −3.06 to −0.17; $P = 0.068$), and both the ITT and PP analyses of the change from baseline in 9-point partial Mayo scores, used to compensate for patients without end of study endoscopies, significantly favored CBD-rich botanical extract (ITT treatment difference = −1.01; 90%CI: −1.98 to −0.04; $P = 0.087$; PP treatment difference = −1.53; 90% CI: −2.73 to −0.33; $P = 0.038$) (Fig. 5).

Mean baseline fecal calprotectin levels were very similar between the CBD-rich botanical extract and placebo groups at 490.6 µg/g and 462.3 µg/g, respectively. For those patients with data available, based on the adjusted mean change from baseline, both treatment groups showed a decrease in fecal calprotectin, and the difference between the groups was not significant (treatment difference = 3.7; 90% CI: −116.8 to 124.2; $P = 0.959$) (Fig. 6). Analysis of the PP analysis set also failed to achieve significance. It should, however, be noted that 600 µg/g was the upper level of detection for the test employed in this trial, and the value of 600 µg/g was imputed for any results that reached or superseded it. Out of the 105 fecal calprotectin tests performed during the study, 65 (equating to 62%) were above the level of detection, with little difference between the CBD-rich botanical extract and placebo groups.

Levels of the circulating inflammatory cytokines IL-2, IL-6, and TNF-α had also all reduced at the end of the treatment period for both treatment groups. Greater reductions were associated with CBD-rich botanical extract, although none were statistically significant for either the ITT or PP analysis sets (data not shown).

Safety

Treatment related AEs were reported by 90% of patients randomized to CBD-rich botanical extract, compared with 48% randomized to placebo (Table 2). The nervous system was most frequently affected by AEs, in particular dizziness and somnolence, of which a high proportion were treatment-related and occurred at a higher incidence in patients taking CBD-rich botanical extract. In comparison, the gastrointestinal system,

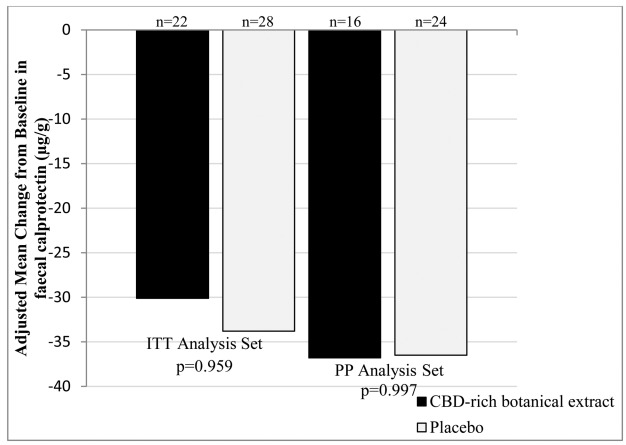

FIGURE 6. Fecal calprotectin levels: change from baseline to final visit—ITT and PP analyses.

which was the second-most commonly affected system, had a higher proportion of AEs that were considered unrelated to study treatment. AEs associated with possible disease progression including colitis, UC, and abdominal pain were all more prevalent in patients taking placebo (42%) than in those taking CBD-rich botanical extract (10%).

The majority of AEs were mild or moderate in severity. The severe AEs that were reported mirrored the overall distribution of AEs; 3 (10%) patients on CBD-rich botanical extract developed severe neurological AEs (1 with disturbance in attention; 1 with dizziness; and 1 with dizziness, joint swelling, and muscle twitching), while 1 patient (3%) on placebo developed a severe gastrointestinal AE (hemorrhagic diarrhea). There were 3 treatment-emergent serious AEs (SAEs) reported, all in patients randomized to placebo; most were suggestive of worsening disease within the placebo group (2 of the 3 reported SAEs were UC, the third was chest pain), and none were treatment related. Additionally, 2 patients became pregnant while participating in the study. The first patient was randomized to placebo; she reported her pregnancy on day 36 of the study and immediately stopped taking study medication. Approximately 4 months later, a post-treatment SAE of fetal growth restriction was recorded which subsequently led to an SAE of stillbirth. The second, randomized to CBD-rich botanical extract, reported her pregnancy on Day 38 of the study and immediately stopped taking study medication. She went on to have a normal pregnancy and delivered a healthy baby with no maternal complications.

Approximately twice as many patients in the CBD-rich botanical extract group stopped study medication due to AEs compared to those in the placebo group (13 [45%] patients and 7 [23%] patients, respectively). This difference was more marked

TABLE 2: Adverse Events by Primary System Organ Class and Preferred Term Reported by Patients at an Incidence of 10% or Greater in Either Treatment Group, by Causality

	All Causality Number (%) of Patients		Treatment-Related Number (%) of Patients	
System Organ Class Preferred Term	CBD-rich Botanical Extract (n = 29)	Placebo (n = 31)	CBD-rich Botanical Extract (n = 29)	Placebo (n = 31)
Total patients with at least one AE	***29 (100)***	***24 (77)***	***26 (90)***	***15 (48)***
Nervous system disorders	**26 (90)**	**11 (35)**	**24 (83)**	**8 (26)**
Dizziness	12 (41)	3 (10)	12 (41)	3 (10)
Somnolence	10 (34)	2 (6)	9 (31)	2 (6)
Disturbance in attention	5 (17)	0	5 (17)	0
Headache	4 (14)	4 (13)	2 (7)	2 (6)
Memory impairment	3 (10)	0	3 (10)	0
Gastrointestinal disorders	**17 (59)**	**17 (55)**	**11 (38)**	**5 (16)**
Nausea	8 (28)	3 (10)	7 (24)	1 (3)
Dry mouth	4 (14)	0	4 (14)	0
Vomiting	4 (14)	0	2 (7)	0
Abdominal pain	1 (3)	5 (16)	0	1 (3)
Colitis ulcerative	1 (3)	5 (16)	0	0
Colitis	1 (3)	3 (10)	0	0
Abdominal distension	0	3 (10)	0	2 (6)
Constipation	0	3 (10)	0	1 (3)
Infections and infestations	**9 (31)**	**3 (10)**	**0**	**0**
Lower respiratory tract infection	3 (10)	0	0	0
Psychiatric Disorders	**9 (31)**	**1 (3)**	**7 (24)**	**1 (3)**
Disorientation	4 (14)	0	3 (10)	0
General disorders and administration site conditions	**8 (28)**	**7 (23)**	**6 (21)**	**3 (10)**
Fatigue	4 (14)	4 (13)	4 (14)	3 (10)
Musculoskeletal and connective tissue disorders	**6 (21)**	**3 (10)**	**4 (14)**	**0**
Back pain	0	3 (10)	0	0
Skin and subcutaneous tissue disorders	**1 (3)**	**6 (19)**	**1 (3)**	**0**
Rash	0	3 (10)	0	0

when treatment-related AEs that caused cessation of study medication were compared (11 [38%] patients on CBD-rich botanical extract compared with 2 [6%] patients in the placebo arm). The predominant AEs causing treatment cessation in the CBD-rich botanical extract group were treatment-related AEs affecting the nervous system, in particular dizziness, which in most cases resolved, while the majority causing treatment cessation in the placebo group were gastrointestinal AEs that were not considered treatment-related, in particular colitis/UC.

There were no notable findings associated with laboratory, ECG, or vital sign assessments.

DISCUSSION

As there is no cure for UC and a proportion of patients with mild to moderate UC do not respond adequately to current therapies, there is a need for alternative treatment options. The pre-clinical evidence for the anti-inflammatory effects of CBD in the gut provided the justification for this proof-of-concept study in a population of patients with UC that had already proven refractory to 5-ASA, which is one of the current mainstays of therapy for mild to moderate disease.

Within this exploratory study, 41% of the patients were deemed to have had insufficient exposure to the study medication to see potential therapeutic benefit, confounding the analysis of the ITT population. To ensure that possible treatment effects seen in patients who had adhered to the protocol were not missed, additional analysis was conducted using the PP analysis set.

The primary endpoint of percentage of patients in remission at the end of treatment was negative. High placebo-remission rates in randomized, controlled clinical trials evaluating therapy for UC are not uncommon,[23] and this study was no exception; placebo remission and responder rates were 25% and 27%, respectively, and CBD-rich botanical extract did not demonstrate superiority for these endpoints. Despite the negative primary endpoint, there were a number of indications to suggest that CBD-rich botanical extract may have been beneficial in the subset of patients who were compliant with the study protocol. It should be noted, however, that in this small population, those secondary endpoints which did reach statistical significance tended to be the more subjective assessments, although greater improvements in total and partial Mayo scores were also seen in patients taking CBD-rich botanical extract compared with placebo.

Although they are subjective, the IBDQ and SGIC are validated measures of patient perception of disease activity, and both demonstrated significant differences in favor of CBD-rich botanical extract.

An important consideration is that the potential effect of CBD-rich botanical extract on gastrointestinal motility might result in an improvement in disease activity scores without a corresponding improvement in inflammation. Although they were small and not statistically significant, the improvements seen in rectal bleeding and endoscopy scores are promising because they act as markers of a true anti-inflammatory effect which, in both cases, were greater on CBD-rich botanical extract than placebo.

Fecal calprotectin levels, a surrogate marker of intestinal inflammation, are increasingly used in clinical practice. A recent study by Kennedy et al (2014) showed that faecal calprotectin levels, in patients diagnosed with IBD, ranged from 532.5 to 2325.0 μg/g.[24] Although fecal calprotectin levels reduced in both groups in this study, the assay employed had an upper limit of detection of 600 μg/g, and many results were above this level. Thus, while no treatment difference was observed, it may have gone undetected due to the insufficient resolution afforded by the assay.

From the data collected during this study, for those patients who did appear to respond to treatment, it was not possible to identify any baseline or other characteristic that differentiated them from the "non-responders," and thus, there was no means of anticipating a particular patient population who might be more likely to respond to CBD-rich botanical extract in future studies.

The overall incidence of AEs in this study was high though, due tot the small sample size and short study duration, it is still possible that there are additional, less common side effects that were not identified but which might be detected through further patient exposure in the future. Overall, there were more AEs in patients taking CBD-rich botanical extract than placebo, with a marked difference in the type and distribution of AEs reported between the 2 treatment groups.

The CBD-rich botanical extract capsules used in this trial were not highly purified and contained a number of other compounds in addition to CBD (notably up to 4.7% THC). Hence, for example, a patient taking 200 mg of the BDS would be taking up to 9 mg or more of THC. A substantial number of AEs reported in the CBD-rich botanical extract group may have been attributable to this THC content. These effects, such as dizziness, nausea, disturbance in attention etc, are likely to have contributed to poor treatment compliance and the higher rate of withdrawals in the active treatment group. Comparatively, there were fewer of these effects in placebo-treated patients. It would be interesting to see how the use of purified CBD study medication might alter the AE profile noted during this study.

Although the majority of neurological AEs were considered to be treatment-related, a higher proportion of the gastrointestinal AEs were not, which can be explained by the study population's underlying UC. Additionally, of the one-third of all AEs that were ongoing at the end of the study, half in the CBD-rich botanical extract group and more than two-thirds in the placebo group were gastrointestinal.

Interestingly, in the placebo group, there were 9 patients with AEs suggestive of worsening colitis (severe hemorrhagic diarrhea, colitis, or UC), compared with only 2 patients on active treatment. This was seen against a backdrop of

stable 5-ASA dosing in both treatment groups, and while it must be viewed with caution, it could be suggestive of a positive treatment effect of CBD-rich botanical extract on the symptoms of UC.

There were a number of limitations; this was a pilot study which aimed to randomize only a small number of patients, and as such, all findings should be interpreted with caution. Due to the exploratory nature of the study, there was little data available upon which to base power calculations and, in retrospect, the sample size calculation expecting a 50% remission rate was rather optimistic. Furthermore, recruitment proved to be very slow; only 60 patients were randomized which was 2 fewer than the target sample size, and this was confounded by a higher-than-expected rate of withdrawals.

There was no central reading to standardize endoscopy scores, which may have resulted in a degree of between-center variation. However, changes in endoscopy scores were seen at similar levels across all of the centers, and in most cases, the endoscopy was performed by the same physician at each center, which largely mitigated within-patient variation. Additionally, the possibility of a "center-effect" was included within the statistical modelling. There were also a number of patients who were missing end of treatment endoscopy scores and, therefore, end of treatment total Mayo scores, primarily because they declined the procedure. In the ITT analysis set, 3 patients in the CBD-rich botanical extract and 1 in the placebo group did not have any end of treatment Mayo score at all, whereas 5 in the CBD-rich botanical extract and 4 in the placebo group were missing end of treatment endoscopy scores and, therefore, only had partial Mayo scores available to compare with baseline. In the PP analysis set, all patients had an end of treatment Mayo score. Though for 3 placebo patients, the lack of an end of treatment endoscopy score meant that this was only a partial score. It is therefore helpful that a previous trial found partial Mayo scores to be equivalent to total Mayo scores in the assessment of remission and response rates.[25]

Every effort was made to ensure that blinding of both the patient and physician was maintained during the study, but no formal assessment was performed, and the high rate of treatment-related AEs that were seemingly linked to the THC content of CBD-rich botanical extract may have had an impact.

Additionally, the higher rate of withdrawals observed in the CBD-rich botanical extract compared with the placebo treatment group may have led to selection bias of a healthier patient population within the active group. Conversely, however, this higher withdrawal rate in combination with poor treatment compliance resulted in a high proportion of patients with insufficient exposure, which may have adversely impacted the ITT primary efficacy analysis.

Going forward, it will be important to review the formulation, titration, and dosing regimen, with the aim of improving tolerability to enable adequate patient exposure to explore efficacy outcomes more fully. In addition, it would be interesting to assess maintenance of remission and relapse rates in a longer placebo-controlled study.

CONCLUSION

This proof-of-concept study represents the first double-blind, randomized, placebo-controlled trial to assess the effect of a CBD-rich cannabis extract in UC. With the exception of the primary endpoint, it was not sufficiently powered to pick up significant differences, but was designed to identify patterns that favor the active treatment. Despite the poor tolerability of the active study medication and the relatively short treatment window, this study suggested that CBD-rich botanical extract may have provided therapeutic benefit to those patients who tolerated it. These findings should be interpreted with caution given the multiple limitations of this study, but they encourage future studies to look at CBD-rich botanical extract. It will be important to review the formulation, titration, and dosing for future studies with the aim of improving tolerability.

ACKNOWLEDGEMENTS

GW sponsored this study and was involved with its design and data collection and analysis. The authors wish to thank GW Clinical Project Managers, Alex Kelly, and Annie Hilliard for their development and oversight of the study from its inception.

REFERENCES

1. Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an english general practice population. *Aliment Pharmacol Ther*. 2000;14:1553–59.
2. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. *Mol Cancer Res*. 2006;4:221–33.
3. Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2016;4:CD000543.
4. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American gastroenterological association institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006;130:935–39.
5. Cherry LN, Yunker NS, Lambert ER, et al. Vedolizumab: an α4β7 integrin antagonist for ulcerative colitis and Crohn's disease. *Ther Adv Chronic Dis*. 2015;6:224–33.
6. Iskandar HN, Dhere T, Farraye FA. Ulcerative colitis: update on medical management. *Curr Gastroenterol Rep*. 2015;17:44.
7. Meier J, Sturm A. Current treatment of ulcerative colitis. *World J Gastroenterol*. 2011;17:3204–12.
8. Ng SC, Kamm MA. Therapeutic strategies for the management of ulcerative colitis. *Inflamm Bowel Dis*. 2009;15:935–50.
9. Potter D. Growth and morphology of medicinal cannabis In: G Guy, B Whittle, eds. *The Medicinal uses of cannabis and cannabinoids.* London: Pharmaceutical Press; 2004.
10. Potter DJ. A review of the cultivation and processing of cannabis (*Cannabis sativa* L.) for production of prescription medicines in the UK. *Drug Test Anal*. 2014;6:31–8.
11. Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in states of inflammation. *Br J Pharmacol*. 2008;153:263–70.
12. Izzo AA. The cannabinoid CB(2) receptor: a good friend in the gut. *Neurogastroenterol Motil*. 2007;19:704–08.
13. Lal S, Prasad N, Ryan M, et al. Cannabis use amongst patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2011;23:891–96.
14. Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend*. 2017;172:9–13.

15. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol*. 2002;42:11S–19S.
16. Capasso R, Borrelli F, Aviello G, et al. Cannabidiol, extracted from cannabis sativa, selectively inhibits inflammatory hypermotility in mice. *Br J Pharmacol*. 2008;154:1001–08.
17. Borrelli F, Aviello G, Romano B, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant *Cannabis sativa*, is protective in a murine model of colitis. *J Mol Med (Berl)*. 2009;87:1111–21.
18. Pertwee RG, Ross RA. Cannabinoid receptors and their ligands. *Prostaglandins Leukot Essent Fatty Acids*. 2002;66:101–21.
19. Marquéz L, Suárez J, Iglesias M, et al. Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue. *Plos One*. 2009;4:e6893.
20. Pertwee RG. Cannabinoids and the gastrointestinal tract. *Gut*. 2001;48:859–67.
21. Izzo AA, Mascolo N, Capasso F. The gastrointestinal pharmacology of cannabinoids. *Curr Opin Pharmacol*. 2001;1:597–603.
22. Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. *Br J Pharmacol*. 2010;160:712–23.
23. Su C, Lewis JD, Goldberg B, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology*. 2007;132:516–26.
24. Kennedy NA, Clark A, Walkden A, et al. Clinical utility and diagnostic accuracy of faecal calprotectin for IBD at first presentation to gastroenterology services in adults aged 16–50 years. *J Crohns Colitis*. 2015;9:41–49.
25. Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14:1660–66.