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ORIGINAL RESEARCH

Efficacy and Safety of Pharmaceutically Manufactured Cannabidiol in Recurrent Pericarditis: A Phase II Clinical Trial

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BACKGROUND: Recurrent pericarditis may be mediated through inappropriate activation of the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome. Pharmaceutically manufactured cannabidiol is an oral formulation that inhibits NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome activation and development of pericarditis in a preclinical model.

METHODS: This Phase 2, open-label, multicenter trial included adult patients with symptomatic recurrent pericarditis: pericarditis chest pain ≥4 on an 11-point numerical rating scale with an elevated C-reactive protein (≥1 mg/dL) or at least mild pericardial inflammation on cardiac magnetic resonance imaging. At enrollment, patients were on stable doses of non-steroidal anti-inflammatory drugs, colchicine, and/or corticosteroids. Cannabidiol was administered during an 8-week treatment period and an optional 18-week extension period when background therapy was tapered and discontinued. The primary efficacy end point was change in patient-reported pericarditis pain. Secondary end points included normalization of C-reactive protein and percentage of patients with recurrences.

RESULTS: Among 27 patients (18 women, mean age 53 years), baseline maximal numerical rating scale pain score was 5.8±1.7, and 10 patients had elevated C-reactive protein. At Week 8, maximal numerical rating scale pain score was 2.1±1.8, and median time to numerical rating scale score ≤2 was 5 days. Among the 10 patients with baseline C-reactive protein elevation, C-reactive protein was normal at Week 8 in 8 patients (80%). During the extension period, 17 (71%) of 24 patients remained free of pericarditis recurrence. A serious adverse event leading to cannabidiol discontinuation occurred in 1 patient.

CONCLUSIONS: In symptomatic patients with recurrent pericarditis, pharmaceutically manufactured cannabidiol appears safe and associated with reductions in pericarditis pain and systemic inflammation.

REGISTRATION: URL: clinicaltrials.gov; Unique Identifier: NCT05494788.

Key Words: cannabidiol ■ clinical trial ■ inflammation ■ pericarditis

Recurrent pericarditis is a debilitating disease with marked reductions in quality of life attributable to multiple flares and fear of recurrence.[1–3] Defined as a relapse of disease following at least a 4 to 6 week symptom free period, recurrent pericarditis occurs in up to 30% of patients following the initial episode of acute pericarditis, and as many as half of these patients will experience multiple recurrences.[4,5]

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CLINICAL PERSPECTIVE

What Is New?

- This phase 2 trial supports the efficacy and safety of pharmaceutically manufactured cannabidiol in recurrent pericarditis, as evidenced by reductions in pericarditis pain scores and C-reactive protein at 8 weeks, the ability of most patients to taper background therapies during the extension period, and favorable overall tolerability with mainly self-limited diarrhea and rash as the most common side effects.

What Are the Clinical Implications?

- Pharmaceutically manufactured cannabidiol may represent a paradigm shift in the treatment of patients with recurrent pericarditis, offering an efficacious, orally administered therapeutic option before escalation to corticosteroids and parenterally administered interleukin-1 blocking agents which carry a high risk of pericarditis recurrence upon discontinuation.
- Future studies are required to determine the role of pharmaceutically manufactured cannabidiol as second-line therapy, in lieu of corticosteroid and interleukin-1 blocker therapy, and if previously demonstrated NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome attenuation using this therapy may allow de-escalation from parenteral interleukin-1 blocker therapy to oral therapy.

Nonstandard Abbreviations and Acronyms

IL-1β	interleukin-1 beta
IL-6	interleukin-6
NRS	numerical rating scale

Approximately 37 000 people in the United States suffer from recurrent pericarditis with a yearly incidence of 6.0 cases per 100 000 people and a median disease duration of several years.[2] Accordingly, effective and safe treatments to resolve acute flares and prevent recurrence are needed.[6]

Inappropriate activation of the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 inflammasome appears central in initiating and sustaining pericardial inflammation,[7] and current effective treatments for recurrent pericarditis inhibit this pathway.[8,9] Cannabidiol is known to have anti-inflammatory properties and may attenuate the innate immune response that perpetuates recurrent pericarditis. Specifically, cannabidiol attenuates NLRP3 inflammasome activation via inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway.[10,11] Cannabidiol has been shown to significantly inhibit release of the inflammatory cytokines interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) in activated murine macrophages, as well as reduce transcription of NLRP3 and pro-IL-1β, and significantly reduce pericardial thickness and effusion in a mouse model of pericarditis.[12]

Based on this mechanism of action and preclinical data, we hypothesized that cannabidiol would be an effective and safe therapy in active recurrent pericarditis. In this phase 2 pilot trial, the primary objective was to demonstrate reduction in pericardial pain using a standardized numerical rating scale (NRS) as well as assess the safety and tolerability of cannabidiol. Secondary objectives included effects on C-reactive protein and the percentage of patients with pericarditis recurrences during the extension period of the trial.

METHODS

The authors declare that all supporting data are available within the article (and its online Supplemental Material).

Investigational Product

The trial medication (CardiolRx™; Cardiol Therapeutics Inc., Canada) was a pharmaceutically manufactured oral formulation containing cannabidiol in a concentration of 100 mg/mL and free of tetrahydrocannabinol (not detected <5 ppm). Inactive ingredients include medium-chain triglyceride oil and Vitamin E.

Design and Population

This was a Phase 2, open-label, multicenter, single arm pilot clinical trial which was conducted in 8 centers located in the United States with each center enrolling between 1 and 9 patients. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The institutional review board at each trial center approved the trial protocol, and written informed consent was obtained from each patient before any trial-related procedure was performed. The trial was registered with clinicaltrials.gov: NCT05494788.

Male and female adults ≥18 years of age who presented with at least their second episode of symptomatic recurrent pericarditis were considered for participation. A symptomatic recurrence was defined as the presence of at least 1 day with pericarditis

pain ≥4 as evaluated on the 11-point NRS within the prior 7 days of being enrolled, in conjunction with either (a) an elevated C-reactive protein (≥1.0 mg/dL) within the prior 7 days of enrollment or (b) evidence of at least mild pericardial inflammation as assessed by late gadolinium enhancement of the pericardium on cardiac magnetic resonance imaging.[13] The NRS is a validated 11-point instrument used to assess patient-reported pericarditis pain. Zero represents "no pain at all" whereas the upper limit of 10 represents "the worst pain ever possible." The highest score reported in the 7 days before the enrollment visit was used.

At trial enrollment, patients must have been prescribed stable doses of non-steroidal anti-inflammatory drugs, colchicine, and/or corticosteroids (in any combination) to treat the recurrent pericarditis episode. Key exclusion criteria included patients with pericarditis secondary to tuberculosis, neoplastic disease, purulent bacterial disease, radiation therapy, or post-thoracic blunt trauma; primary diagnosis of myocarditis; prior history of sustained ventricular arrhythmias or QT interval prolongation; current diagnosis of cancer with the exception of non-melanoma skin cancer; and immunosuppressive therapy with rilonacept, anakinra, canakinumab, methotrexate, azathioprine, cyclosporine, and/or intravenous immunoglobulin (see Data S1 for a full list of inclusion and exclusion criteria).

Cannabidiol and Concomitant Medication Schedule

Eligible patients received the trial medication upon completion of the screening assessments (i.e., baseline visit). Cannabidiol, which is an oral solution (100 mg/mL), was titrated up to 10 mg/kg twice daily, and patients were maintained at the maximum tolerated dose until completion of the trial. Two periods were defined in the trial: an 8-week treatment period and an 18-week extension period. During the 8-week treatment period, patients received the trial medication in addition to unchanged background therapy for pericarditis. As of Week 8, patients could continue the trial medication during an 18-week extension period. During the extension period, background therapy to treat pericarditis was to be weaned while patients remained on the maximally tolerated trial medication dose. Per the trial protocol, non-steroidal anti-inflammatory drugs were to be weaned within 2 weeks and corticosteroids within 6 weeks of starting the extension period (at investigator discretion, with protocol recommendation to taper by 5 mg prednisone or equivalent every week). For patients not taking corticosteroids, colchicine was to be weaned between 2 and 4 weeks of entry into the extension period, and for those on corticosteroids, colchicine weaning was to occur between Weeks 6 and 8 of the extension period.

Efficacy and Safety End Points

The primary efficacy end point was the change in patient-reported pericarditis pain, using an 11-point NRS pain score, from baseline (highest pain score within the past 7 days of Day 1) to Week 8 (highest pain score during the past 7 days preceding Week 8).

Secondary efficacy end points included percentage of patients for whom C-reactive protein normalized (≤0.5 mg/dL) at 8 and 26 weeks (for patients with C-reactive protein ≥1.0 mg/dL at baseline), NRS pain score at Week 26 (highest pain score during the past 7 days of Week 26), and percentage of patients with pericarditis recurrence during the extension period. Safety parameters included the number of adverse events and serious adverse events, changes in Columbia-Suicide Severity Rating Scale, changes in laboratory parameters including liver function parameters and international normalized ratio, and ECG intervals and rhythm during the 26-week study period.

Statistical Analysis

Statistical analyses were performed using SAS version 9.4. Statistical analyses in this open-label, single-arm trial were descriptive in nature and included data from all enrolled patients. No statistical inference or missing value imputation was performed.

Safety end points were reported over the entire duration of the trial as patient incidence. Summary statistics reported for continuous variables included the number of patients, mean with SD, median with quartile 1 and quartile 3, and minimum and maximum. For categorical variables, frequency and percentage were reported.

For the primary efficacy outcome, which was assessed at the Week 8 visit, the highest 11-point NRS score collected on the daily NRS questionnaire for the 7 days before the Week 8 visit (or planned visit date if Week 8 visit not performed) was used. The change in patient-reported pericarditis pain using an 11-point NRS from baseline to 8 weeks was analyzed as a continuous variable.

RESULTS

In total, 27 patients were enrolled between January 09, 2023, and March 04, 2024, and all 27 patients were included in the analyses (Figure 1). Of these patients, 18 (66.7%) were women, and the mean age was 53±15 years. Average disease duration and the number of pericarditis episodes per year before trial entry were 2.7 years and 5.8 events per year, respectively. The mean highest NRS pain score in the 7 days preceding the baseline visit was 5.8±1.7 points. Mean baseline C-reactive protein level was 2.0 mg/dL with elevated

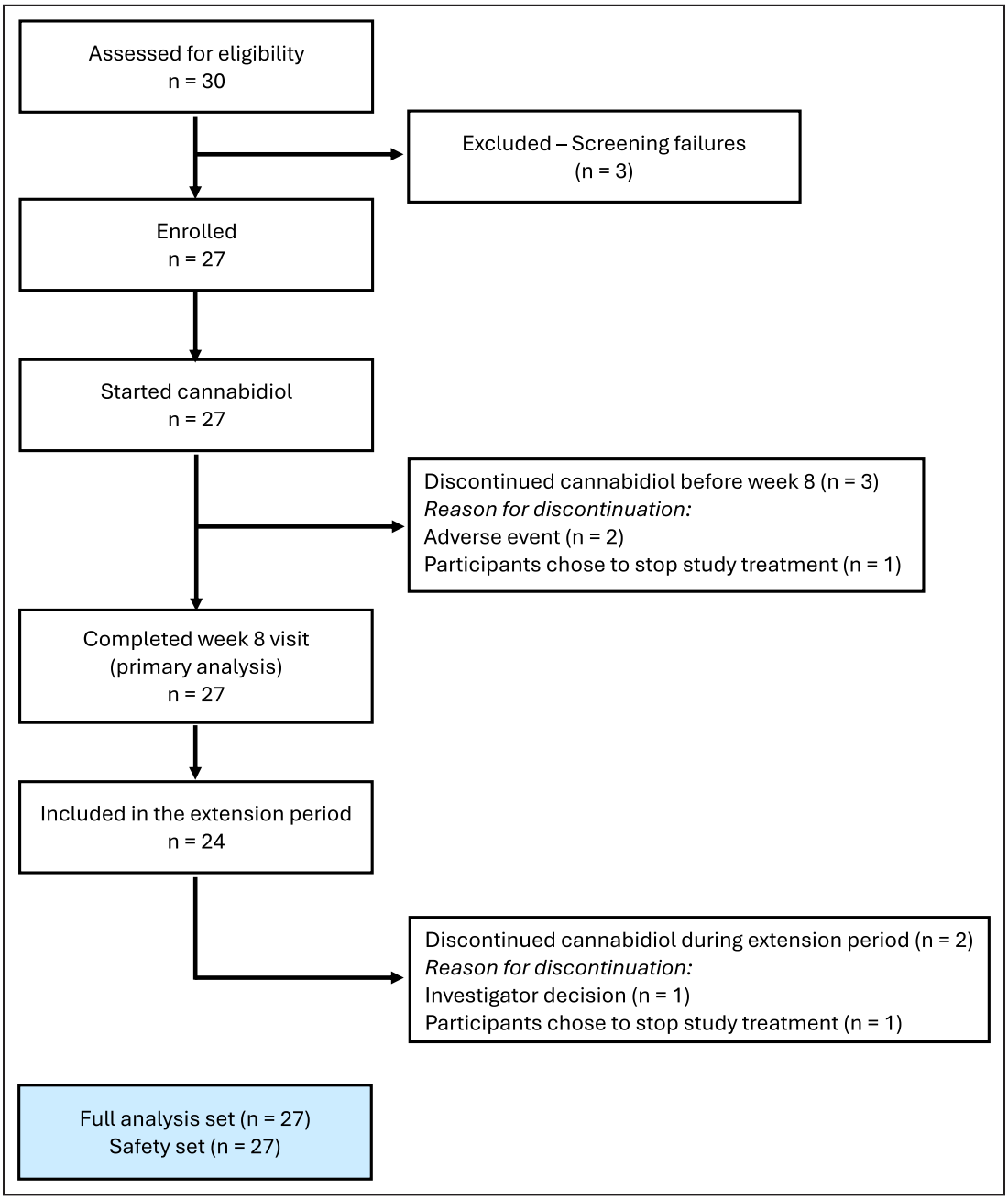

Figure 1. Trial profile.

C-reactive protein (≥1.0 mg/dL) in 10 patients (37.0%). Pericardial effusion was reported in 21 patients (77.8%), pericardial rub in 4 patients (14.8%), and ST-segment elevation or PR-segment depression in 5 patients (18.5%). Background pericarditis therapy at enrollment included colchicine in 23 (85.2%), non-steroidal anti-inflammatory drugs in 18 (66.7%), and corticosteroids in 11 (40.7%) patients (Table 1). Of these, 19 patients (70.4%) received combination therapy, 3 patients (11.1%) received a combination of all 3 medication classes, and 5 patients (18.5%) received a single agent.

Pericardial NRS Pain Score

The primary outcome was assessed at the Week 8 visit. The mean highest NRS pain score in the 7 days preceding the Week 8 visit was 2.1±1.8 which resulted in a mean change from baseline of −3.7 points (Figure 2). The median time to resolution of pericardial pain as assessed by an NRS score of ≤2 was 5 days. During the extension period, the NRS pain score continued to decrease—the mean NRS score at the Week 26 visit was 1.5±2.2, representing a 4.3±2.5-point decrease from the baseline visit (Figure 3).

Table 1. Baseline Demographics and Clinical Characteristics

Demographic and clinical characteristics of the patients at baseline	All patients enrolled (n=27)
Age, y; mean±SD	52.7±15.0
Women, n (%)	18 (66.7)
Race: White, n (%)	27 (100.0)
Ethnicity Non-Hispanic or Latino, n (%)	27 (100.0)
Previous episodes of pericarditis, n (%)	
2 episodes	9 (33.3)
3 episodes	9 (33.3)
4 episodes	4 (14.8)
>4 episodes	5 (18.5)
Symptoms present at time of diagnosis (not mutually exclusive), n (%)	
New widespread ST-segment elevation or PR-segment depression according to ECG findings	5 (18.5)
Pericardial effusion (new or worsening)	21 (77.8)
Pericardial rub	4 (14.8)
Pericarditis chest pain	25 (92.6)*
Medications used to treat pericarditis, n (%)	
Colchicine	23 (85.2)
NSAIDs	18 (66.7)
Corticosteroid	11 (40.7)
Maximum NRS pain score at baseline	5.8±1.7
C-reactive protein at baseline, mg/dL	2.0±4.9
Pericarditis before enrollment	
Duration of pericarditis, y	2.7
Pericarditis events per y, mean	5.8

Data are means ± SD or number of patients (percentage).
NRS indicates numerical rating scale.
*2 patients who had an NRS score ≥4 at visit 1 did not have chest pain at the time of diagnosis.

C-Reactive Protein

C-reactive protein levels for the entire group of patients were reduced from a mean of 2.0±4.9 mg/dL at baseline to 0.7±2.5 mg/dL (mean) at Week 8 and 0.6±1.3 mg/dL (mean) at Week 26 (Figure 4). C-reactive protein elevation (C-reactive protein ≥1.0 mg/dL) was noted in 10 patients at or within 7 days before the baseline visit. Among these 10 patients, C-reactive protein normalization (C-reactive protein ≤0.5 mg/dL) was seen in 8 patients (80%) at Week 8. The 2 patients who did not normalize their C-reactive protein included one patient with an initial C-reactive protein of 24.2 mg/dL in whom C-reactive protein improved steadily to reach 1.1 mg/dL by Week 8. This likely reflected a high baseline severity of pericardial inflammation that responded to therapy slower than expected. The second patient had complete symptomatic resolution (NRS score of 0) without recurrence, but an initial C-reactive protein of 4.6 mg/dL, which remained elevated at 13.1 mg/dL at Week 8. A diagnosis of COVID-19 was made 2 weeks later, and C-reactive protein levels normalized at Weeks 16 and 26. Both patients completed the extension period and were asymptomatic with normalization of C-reactive protein at the end of the trial.

Among the patients with an elevated C-reactive protein at baseline, C-reactive protein decreased from a mean of 5.7±7.7 mg/dL to a mean of 0.3±0.4 mg/dL at Week 8, representing a mean decrease of 5.4 mg/dL over the initial treatment period. For the majority of patients, the first post-enrollment C-reactive protein measurement occurred at Week 3. Of the 8 patients whose C-reactive protein normalized, 5 (62.5%) had normalized by Week 3 and 6 (75.0%) had normalized by Week 4 and maintained a normalized C-reactive protein at Week 8.

Background Therapy Weaning

In total, 24 patients (88.9%) continued in the extension period. For the 3 patients who did not continue in the extension period, the trial medication was stopped prematurely because of an adverse event (n=2) or failure to respond (n=1) before the Week 8 visit.

During the extension period of the trial, 17 (70.8%) of 24 patients remained free of a new recurrence of pericarditis. This represented a reduction in the pericarditis events in the trial population from 5.8 events per year before trial enrollment to 0.9 events per year during trial involvement. Among the 7 patients with pericarditis recurrence, 3 had an elevated C-reactive protein within 7 days before their baseline visit and 5 were on corticosteroid therapy at baseline. All were managed with escalation of prior background therapy.

Of the 5 patients taking corticosteroids who had a recurrence on weaning, 3 were subsequently weaned off corticosteroids, completing the trial on a combination of colchicine, non-steroidal anti-inflammatory drugs, and cannabidiol. One patient required continued corticosteroids despite a reattempt at weaning and one patient transitioned to rilonacept.

Safety and Tolerability

Overall, the trial medication was well tolerated. Most patients (n=20, 74.1%) were treated with 10 mg/kg twice daily. For 4 patients (14.8%) the maximally tolerated dose was 7.5 mg/kg twice daily and for 3 patients (11.1%) the maximally tolerated dose was 5 mg/kg twice daily. Complete data were collected for all 27 patients in the treatment period and for the 24 patients in the extension period.

The most frequently reported adverse events are displayed in Table 2. The trial medication was discontinued for 4 patients who sustained at least 1 adverse event and was reduced and/or temporarily interrupted

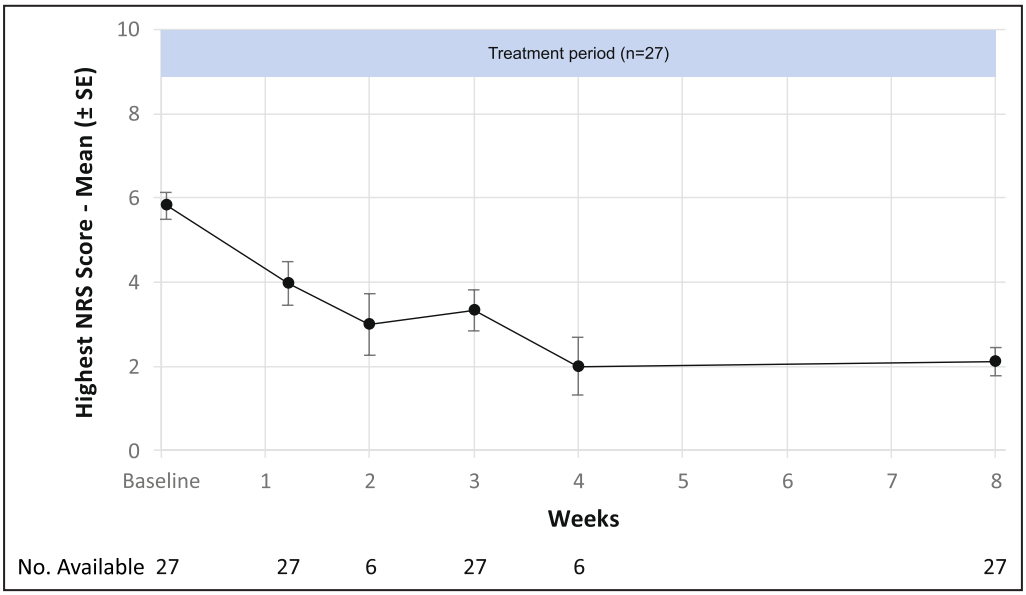

Figure 2. Highest NRS score by week during the treatment period.
At baseline, maximal NRS pain score was 5.8±1.7. The primary outcome was assessed at Week 8, and was 2.1±1.8, resulting in a mean decrease from baseline of 3.7 points. Error bars are SE. NRS indicates numerical rating scale.

for 8 patients because of the occurrence of an adverse event.

No clinically important change in the QTc interval was observed between enrollment and the last follow up visit (417±23 versus 423±22 milliseconds). No patients experienced suicidal ideation or behavior as assessed by the Columbia-Suicide Severity Rating Scale through to the end of trial. The most common adverse event was diarrhea occurring in 15 patients, in 10 of whom it was self-limited. Rash occurred in 8 patients, 2 of whom required dose reduction of the trial medication, 3 required concomitant antihistamine therapy, and 3 required topical corticosteroid use. Rash resolved in all but 2 patients in whom the rash was atypical and considered by the investigator to be not or unlikely related to the trial medication.

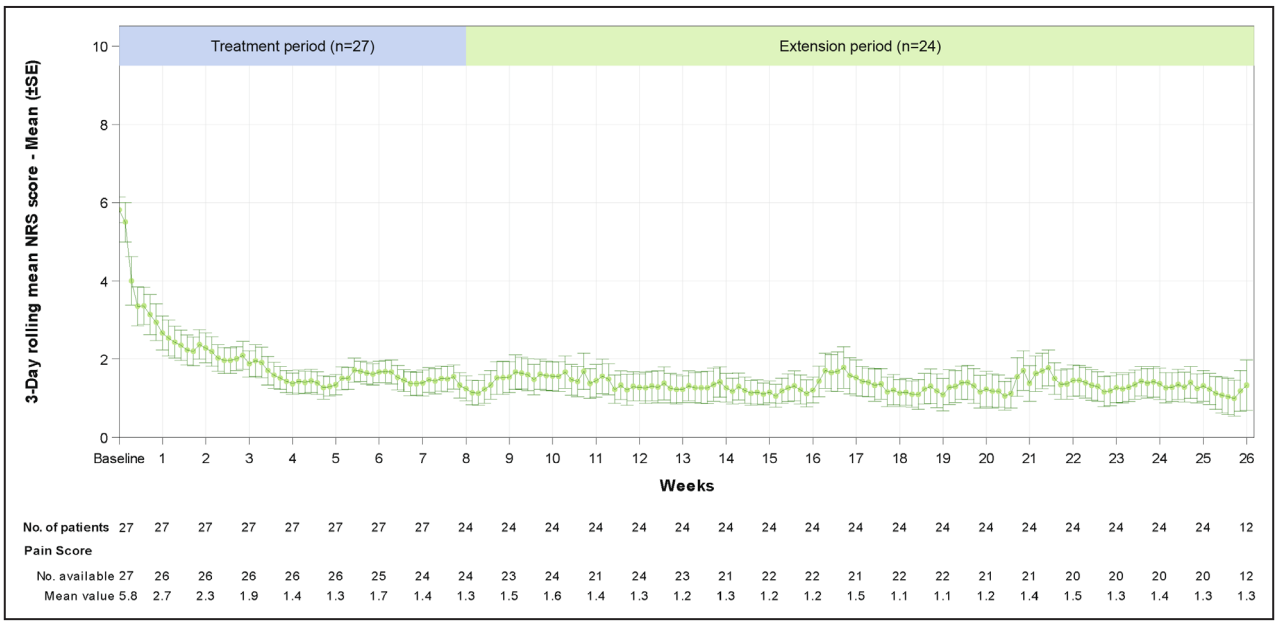

Figure 3. Three-day rolling mean NRS score by week during the treatment and extension periods.
The 3-day rolling mean was calculated on the basis of non-missing values over each successive 3-day interval. Error bars are SE. NRS indicates numerical rating scale.

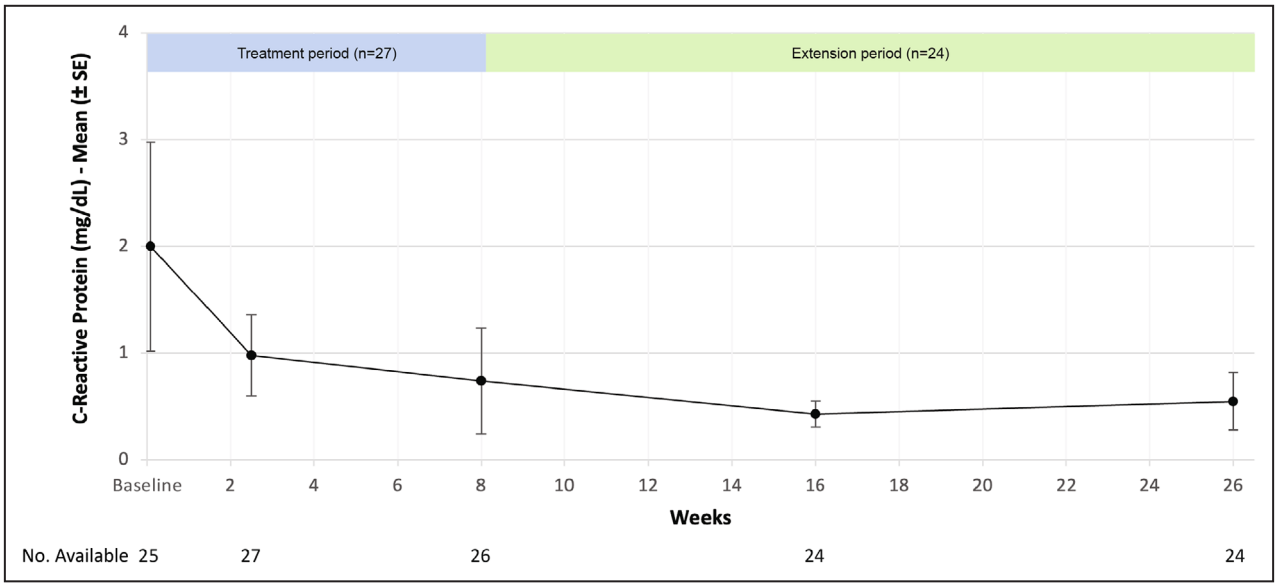

Figure 4. C-reactive protein by week during the treatment and extension periods.
C-reactive protein levels for the entire group of patients were reduced from 2.0±4.9 mg/dL at baseline to 0.7±2.5 mg/dL at Week 8 and 0.6±1.3 mg/dL at Week 26. Error bars are SE. mg/dL indicates milligram per deciliter.

Serious adverse events occurred in 2 patients. This included 1 patient with a probable Drug Reaction with Eosinophilia and Systemic Symptoms syndrome considered by the investigator to be possibly related to trial medication on a background history of hypersensitivity reactions and who was concurrently started on a medication (celecoxib) known to cause Drug Reaction with Eosinophilia and Systemic Symptoms syndrome. In this patient, both trial medication and celecoxib were discontinued, antihistamines instituted, oral prednisone dosing escalated to 50 mg daily for 1 week before a slow taper, and topical steroid added. The other patient experienced serious adverse events which were not considered by the investigator to be related to the trial medication: a tooth fracture requiring admission for bridging anticoagulation before extraction, with hospital admission complicated by viral gastroenteritis, and who subsequently experienced chest pain.

Table 2. Treatment Emergent Adverse Events With More Than 3 Events Reported Over the Entire Study Period

MedDRA preferred term	Patients with at least 1 event, n (%)	Events reported
Diarrhea	15 (55.6)	20
Chest pain	10 (37.0)	13
Rash	8 (29.6)	8
Nausea	5 (18.5)	9
Upper respiratory tract infection	5 (18.5)	7
Fatigue	5 (18.5)	5
Abdominal discomfort	4 (14.8)	4
Headache	4 (14.8)	4

DISCUSSION

Pharmaceutically manufactured cannabidiol is an oral formulation containing no detectable tetrahydrocannabinol. The active ingredient is currently approved by the US Food and Drug Administration for treatment of seizures in patients 1 year of age and older with certain rare epilepsy or genetic disorders. Cannabidiol attenuates multiple intracellular inflammatory signaling pathways, including inhibiting activation of the NLRP3 inflammasome via inhibition of NF-kB and may reduce inflammasome priming. Cannabidiol reduced transcription of pro-IL-1β and NLRP3 and also decreased levels of IL-1β and IL-6, as well as reducing pericardial thickness and effusion in a preclinical model of pericarditis.[10,12]

The results of our trial show that pharmaceutically manufactured cannabidiol reduced pericarditis NRS pain score and resulted in C-reactive protein normalization in a majority of patients. Cannabidiol also facilitated weaning of background pericarditis medications and was generally well tolerated in most patients.

The trial population represented a high-risk, predominantly colchicine-refractory, population with a pericarditis event rate of 5.8 events per year before trial enrollment. Background medical therapy utilized in this trial population included colchicine use in 85.2% and corticosteroid use in 40.7% of patients. Colchicine use was similar to the prior randomized withdrawal IL-1 blocker trials Anakinra—Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP)[14] and Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes

Study (RHAPSODY),[15] where colchicine use was 85.7% and 80.0%, respectively. Corticosteroid therapy use was similar to the RHAPSODY study (49.0%), but lower than that seen in the AIRTRIP trial where corticosteroid-dependence was required for enrollment. The background pericarditis recurrence event rate in this trial (5.8 events per year) was comparable to recent trials using IL-1 blockers in recurrent pericarditis patients. Phase 2 and 3 clinical trials utilizing rilonacept in recurrent pericarditis reported means of 3.9 and 4.4 background events per year, respectively. Similarly, the AIRTRIP trial investigated the use of anakinra in recurrent pericarditis and reported a median of 6.8 recurrences and disease duration of 27.8 months at the time of trial enrollment.

The efficacy of recurrent pericarditis treatment with pharmaceutically manufactured cannabidiol is supported by NRS pain score reduction, C-reactive protein normalization, and reduction in the event rate with treatment versus event rate before treatment commencement. Mean NRS pain score reduction of 3.7 points with a median time to resolution or near resolution of pericarditis pain of 5 days in this trial population were comparable to those in recent IL-1 blocker trials. A similar NRS pain score reduction of 4 points and median 5 days to symptomatic resolution or near resolution from treatment commencement was reported in the phase 3 RHAPSODY trial utilizing rilonacept. The AIRTRIP trial utilized a different pain scoring system and reported a reduction of pain from 7.7 to 0.4 using the visual analog scale.

Among the trial sub-group with elevated C-reactive protein at baseline, the mean C-reactive protein of 5.7 mg/dL in this trial was comparable to the 4.2 and 6.2 mg/dL seen in the AIRTRIP and RHAPSODY trials, respectively. In the current trial, C-reactive protein normalization was seen in 80% of the trial population with a mean C-reactive protein of 0.3 mg/dL at Week 8. This C-reactive protein normalization was lower compared to AIRTRIP, where all patients had C-reactive protein normalization, and RHAPSODY, where 96.5% had C-reactive protein normalization. Differences in trial therapy mechanism of action, route of administration, and the small sample size in this trial may account for the differences seen in rates of C-reactive protein normalization.

Nonetheless, the efficacy of therapy is supported by the ability to maintain freedom from recurrence in 70.8% of patients despite weaning background therapy, and a decrease in the event rate from 5.8 events per year before trial enrollment to 0.9 events per year during trial involvement. Although event rates during this trial were higher than the 0.04 events per year in the rilonacept treatment group, these are still markedly lower than the 2.18 events per year seen in those patients who suspended rilonacept following 18 months of therapy.[16] It is also noteworthy that recurrence during weaning of background therapy was more common among patients receiving corticosteroid therapy at baseline. In these patients, rescue with reinstitution of background therapy in combination with cannabidiol allowed clinical resolution of the recurrent pericarditis flare and subsequent weaning of corticosteroid therapy. This suggests that weaning of corticosteroid therapy may need to be performed slower than protocols utilized in IL-1 blocker trials.

Pharmaceutically manufactured cannabidiol was well tolerated, with diarrhea and rash being the most common adverse effects. Despite this, maximal doses of trial medication were utilized in 74.1% of patients, and trial medication discontinuation occurred in only 11.1% of patients because of adverse events. Gastrointestinal side-effects were minimized by advice to take the trial medication with high-fat meals. Of those patients who experienced diarrhea, 12 received concomitant baseline treatment with colchicine. A recent meta-analysis reports diarrhea in 17.9% of patients treated with colchicine.[17] The mechanism of this adverse colchicine effect is unclear but is thought to be both directly and centrally mediated, acting through stimulation of prostaglandin synthesis, increased biliary and intestinal secretion, and changes in mucosal function.[18] The mechanism of cannabidiol-induced diarrhea is also multifactorial and poorly understood. It is thought to involve the endocannabinoid system, particularly in the enteric nervous system, and induction of intestinal motility.[19] The complex interplay of multiple diarrhea-inducing pathways likely exacerbated the incidence of diarrhea compared with single-agent therapy. Cannabidiol-induced erythematous, pruritic, papular skin rashes have been previously described with corresponding histology demonstrating papillary dermal edema, lymphohistiocytic infiltrates and sparse eosinophils involving the perivascular and periadnexal area.[20] Rashes seen in this trial were successfully managed with trial medication dose reduction, with or without the use of concomitant antihistamine therapy and/or topical corticosteroid use. One patient required discontinuation of trial medication for the diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms syndrome on a background history of hypersensitivity reactions and who was concurrently started on celecoxib, which is known to cause Drug Reaction with Eosinophilia and Systemic Symptoms syndrome.

Pending future investigations, pharmaceutically manufactured cannabidiol may represent a paradigm shift in the treatment of patients with recurrent pericarditis, offering an efficacious, orally administered therapeutic option before escalation to parenterally administered IL-1 blocking agents. The results of this trial demonstrate the ability to wean background therapy among difficult to treat, colchicine-refractory patients with recurrent pericarditis with a promising, low event rate on cannabidiol monotherapy. Contemporary guidelines recommend

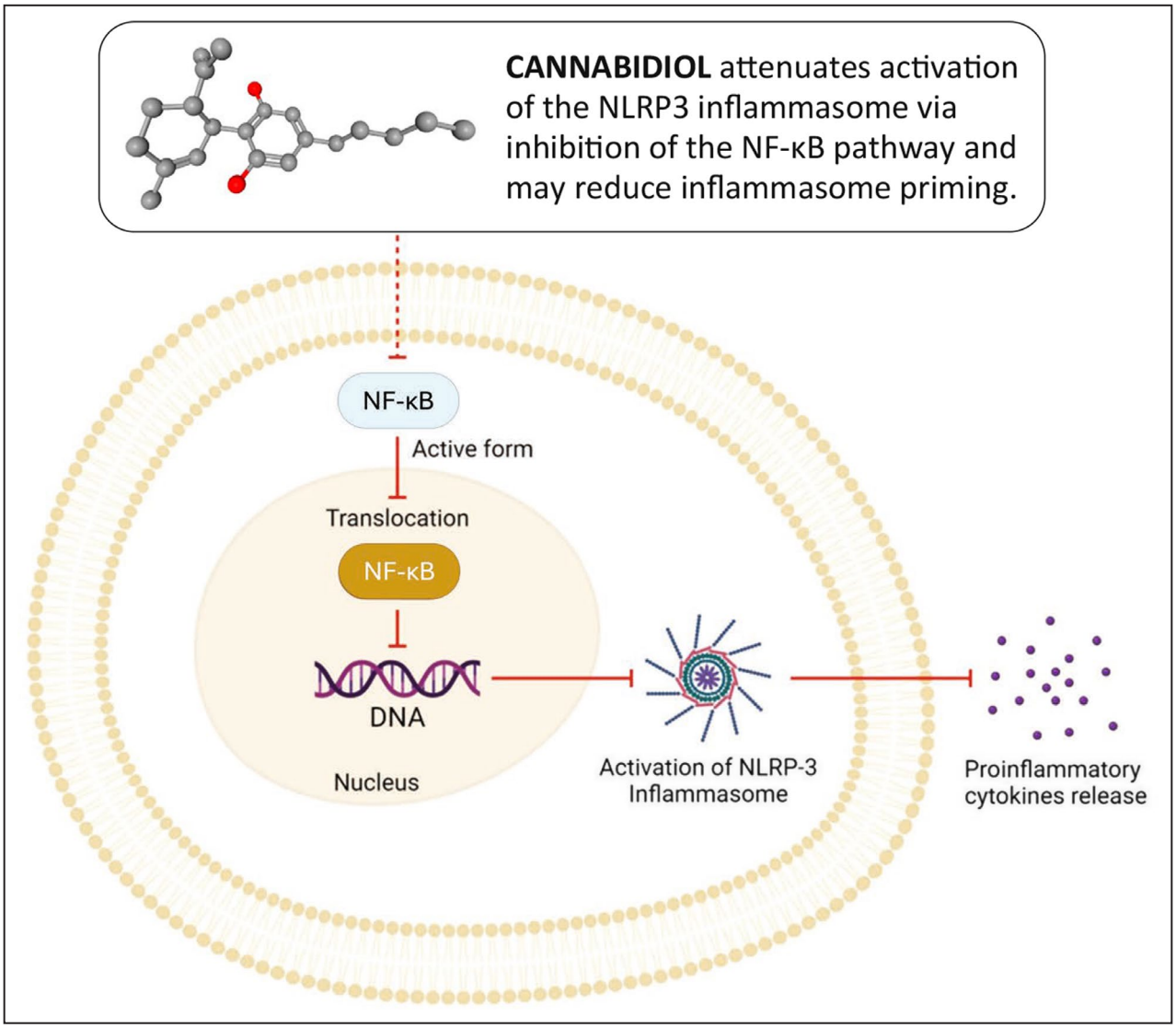

Figure 5. Putative mechanism of action of cannabidiol, a novel modulator of inflammasome signaling.
Stressors or injurious stimuli (eg, viral infection; tissue damage) trigger activation of the inflammasome pathway. In response, proinflammatory cytokines are released (eg, IL-1; IL-6). These cytokines contribute to the development and progression of pericarditis. Cannabidiol attenuates NLRP3 inflammasome activation via inhibition of the NF-κB pathway and results in decreases in IL-1β and IL-6. By targeting and down-regulating activation of these pathways, cannabidiol may provide a novel approach to the treatment of pericarditis. IL-1 indicates interleukin-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; and NLRP3, NACHT, leucine-rich repeat, and pyrin domain-containing protein 3. Adapted from Naya et al[23] with permission. Copyright ©2024, Taylor & Francis.

either corticosteroid therapy or IL-1 blockers as second-line therapy in recurrent pericarditis.[4,5] However, corticosteroids are associated with both significant side effects and a high risk of pericarditis recurrence.[5,21] Pharmaceutically manufactured cannabidiol offers a promising alternative to corticosteroids as second-line therapy in the treatment of recurrent pericarditis. Similarly, IL-1 blockers are associated with a high rate of pericarditis recurrence following discontinuation of IL-1 blockade.[16,22] Attenuation of NLRP3 inflammasome activation via inhibition of the NF-κB pathway and resulting decreases in IL-1β and IL-6 (the probable mechanism of action of cannabidiol; Figure 5[23]), rather than isolated blockade of the IL-1 pathway may offer the ability to de-escalate parenteral IL-1 blocker therapy to oral therapy in this population. However, this hypothesis requires investigation (via the ongoing phase 3 CardiolRx in Recurrent Pericarditis [MAVERIC] [trial; NCT06708299]), but if successful, may offer a different treatment for patients instead of long-term IL-1 blockers.

Limitations

Several limitations should be noted. This was an open-label, single-arm clinical trial with a small sample population. As a result, by design the sample size and

absence of a comparator group limits interpretation of patient outcomes and potential subgroup analyses. Although similar to a prior phase 2 trial in recurrent pericarditis, this trial's generalizability is limited both by the sample size and patient demographics, including ethnicity, and by the relatively short 18-week extension period, which constrains evaluation of long-term pericarditis remission.[24] Additionally, heterogeneity of baseline therapy and disease duration could also have impacted result interpretation. These limitations will be addressed in upcoming Phase 3 trials involving a larger cohort of patients and a comparator placebo group. Cardiac imaging evaluations including echocardiography and cardiac magnetic resonance imaging to assess the severity of pericarditis were not mandated, but as discussed, patient characteristics were similar to prior randomized withdrawal trials of IL-1 blockers. Finally, additional inflammatory cascade biomarkers, including IL-1β, RelA (NF-κBp65) and NLRP3, were not assessed to further elucidate the potential mechanism of action of cannabidiol in recurrent pericarditis.

CONCLUSIONS

In symptomatic patients with recurrent pericarditis, treatment with pharmaceutically manufactured cannabidiol resulted in reductions in pericarditis pain and systemic inflammation (as assessed via C-reactive protein). The majority of patients remained free of recurrence during the extension period with weaning and discontinuation of background pericarditis medications. The trial medication was safe in this small sample size with a serious adverse event in one patient that resulted in discontinuation of treatment. Overall, these findings support larger, definitive randomized controlled trials evaluating the efficacy and safety of pharmaceutically manufactured cannabidiol in pericarditis.

ARTICLE INFORMATION

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Supplemental Material

Data S1. Supplemental Methods
TREND Checklist

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