ESC HEART FAILURE
ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14889

STUDY DESIGN

Impact of cannabidiol on myocardial recovery in patients with acute myocarditis: Rationale & design of the ARCHER trial

Dennis M. McNamara[1], Leslie T. Cooper[2], Yaron Arbel[3], Arvind Bhimaraj[4,5], Edimar Bocchi[6], Matthias G. Friedrich[7,8,9], Matthieu Kerneis[10,11,12], Peter Liu[13], Andrea B. Parker[14], Eldon R. Smith[14], W. H. Wilson Tang[15], Guillermo Torre-Amione[16], Carsten Tschöpe[17,18,19]* and On behalf of the ARCHER Study Group

[1]*Center for Heart Failure, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA;* [2]*Department of Cardiovascular Medicine, Mayo Clinic College of Medicine and Science, Jacksonville, Florida, USA;* [3]*Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel;* [4]*Houston Methodist Hospital, Houston, Texas, USA;* [5]*Weill Cornell Medical College, New York, New York, USA;* [6]*Instituto do Coração Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil;* [7]*Departments of Medicine and Diagnostic Radiology, Research Institute of the McGill University Health Centre, McGill University, Montreal, Canada;* [8]*Department of Cardiology, Universitätsklinikum Heidelberg, Heidelberg, Germany;* [9]*Department of Cardiac Sciences and Radiology, University of Calgary, Calgary, Canada;* [10]*Pitié Salpêtrière Hospital, Paris, France;* [11]*Sorbonne University, Paris, France;* [12]*ACTION Study Group, Paris, France;* [13]*University of Ottawa Heart Institute, Ottawa, Canada;* [14]*Cardiol Therapeutics Inc., Oakville, ON, Canada;* [15]*Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA;* [16]*Instituto de Cardiologia, Hospital Zambrano-Hellion, Escuela de Medicina y Ciencias de la Salud, Tecnologico de Monterrey, Monterrey, Mexico;* [17]*Department of Cardiology, Angiology and Intensive Medicine, Deutsches Herzzentrum der Charité (DHZC), Campus Virchow (CVK), Berlin, Germany;* [18]*Berlin Institute of Health (BIH) at Charité – Center for Regenerative Therapies (BCRT), Berlin, Germany; and* [19]*German Center for Cardiovascular Research (DZHK); Partner Site Berlin, Charité University, Berlin, Germany*

Abstract

Aims Acute myocarditis, although a rare disease, can be associated with sudden cardiac death or the need for transplantation in both children and young adults. To date, there is no definitive evidence to support the routine use of immunosuppressive therapy or treatment targeting inflammation in patients with myocarditis. Animal models of cardiovascular (CV), as well as neurological diseases, have demonstrated that cannabidiol has significant anti-inflammatory properties and may represent a promising therapy in acute myocarditis. This efficacy has been shown in a murine model of autoimmune myocarditis as well as in in vitro and in vivo models of heart failure (HF).

Methods and results We present the rationale and design of the ARCHER Trial, an international multicentre, double-blind, randomized, placebo-controlled, phase II study examining the safety and efficacy of a pharmaceutically produced cannabidiol formulation, in patients with mild to moderate acute myocarditis. Eligible patients are those with acute myocarditis, randomized within 10 days of the diagnostic cardiac MRI (CMR), which has met defined diagnostic criteria for myocarditis. Oral treatment (cannabidiol or placebo) is titrated from 2.5 mg/kg of body weight up to 10 mg/kg of body weight b.i.d. (or highest tolerated dose) and taken for 12 weeks in addition to standard of care therapy for HF. The primary endpoints are defined as changes in global longitudinal strain (GLS) and extra cellular volume (ECV), measured by CMR at 12 weeks. Assuming 80% power, a 5% alpha risk and 25% missing CMR follow-up data at Week 12, 100 patients are required to demonstrate the desired treatment effect of 18%. The change in left ventricular ejection fraction (LVEF) from baseline to Week 12 was selected as the secondary endpoint. Additional exploratory endpoints include changes in hs-troponin, NT-proBNP, markers of inflammation and endothelial function during the 12-week treatment period. The trial is ongoing but is now more than 50% recruited. As enrolment in the trial continues, no interim data are available for inclusion in this Design paper.

Conclusions The ongoing ARCHER Trial is an international, multicentre, double-blind, randomized, placebo-controlled phase II study, designed to determine the effect of a pharmaceutically produced cannabidiol formulation on CMR parameters in patients presenting with acute myocarditis. Enrolment of 100 patients is expected to conclude in Q3 2024. Study results will be available in early 2025.

Keywords Anti-inflammatory; Cannabidiol; CMR; Myocarditis; Randomized trial

Received: 10 April 2024; Revised: 10 May 2024; Accepted: 11 May 2024
**Correspondence to: Carsten Tschöpe, Department of Cardiology, Angiology and Intensive Medicine, Campus Virchow, German Heart Center (DHZC) at Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Email: carsten.tschoepe@dhzc-charite.de*

Introduction

Acute myocarditis is a rare condition characterized by cardiac inflammation which may result in impaired cardiac function, arrhythmias and conduction disturbances. The presentation may be fulminant, requiring pharmacologic or mechanical circulatory support or can result in sudden cardiac death; milder cases can be self-limiting but may progress to dilated cardiomyopathy with eventual chronic heart failure (HF).

Although the aetiology of acute myocarditis is varied, the most common cause is viral infection of the myocardium.[1] Common viruses associated with myocarditis include adenovirus, enterovirus, parvovirus B19, herpes virus, Epstein–Barr virus and cytomegalovirus.[1] Other viruses that uncommonly cause myocarditis include hepatitis C,[2] the human immunodeficiency virus,[1] and the SARS-CoV-2 coronavirus.[3]

In addition to viruses, myocarditis can be triggered by other infectious processes such as Chagas disease, Lyme disease and even diphtheria.[1] Myocarditis can also be precipitated by a large number of chemical entities; examples include the more recently introduced checkpoint inhibitors.[4] Some antipsychotic agents such as clozapine can also induce inflammation in the myocardium.[1] Finally, myocarditis has also been reported in association with a number of clinical syndromes, including reactions to certain drugs, such as penicillin, and secondary to autoimmune diseases such as lupus and Sjogren's disease.

The exact pathophysiology of myocarditis is not completely understood. In viral infection-mediated myocarditis, viral proliferation in myocytes can cause direct tissue injury. However, most tissue damage in myocarditis results from the interaction of the viral trigger with the immune system. The immune response is activated to eliminate virus-infected cells to control the infection. Further, intracellular components released from necrotic myocytes may trigger an autoimmune response by molecular mimicry with viral antigens.[5] It is the autoimmune response that results in continued cell necrosis, inflammation, development of fibrosis and further impairment in cardiac function and is believed to lead to the development of chronic dilated cardiomyopathy. It is acute idiopathic or presumed viral myocarditis with ongoing inflammatory damage to the myocardium that is the focus of the current study.

To date, no specific therapy has been developed with proven efficacy in patients with acute myocarditis. All patients with acute myocarditis should receive guideline-specified medical treatment for HF as indicated by the clinical presentation.[6] This includes ACE inhibitors, ARBs or ARB/NEP inhibitors, beta-blockers, diuretics (including aldosterone inhibitors) and SGLT2 inhibitors. If the presentation is one of fulminant HF, then inotropic support and possibly mechanical circulatory support or veno-arterial extracorporeal life support are indicated.[7] Steroid-based immune suppressive immunomodulating therapies are recommended only for endomyocardial biopsy (EMB)-proven giant cell or eosinophilic myocarditis.

A number of therapeutic approaches have been tested in patients with myocarditis, although the condition remains a therapeutic dilemma.[1] Although intense inflammation in the myocardium serves to eliminate the virus quickly, thereby avoiding more extensive tissue damage, if the inflammation persists despite viral elimination, continued myocardial damage can occur. An effective anti-inflammatory therapy, while limiting tissue damage mediated by inflammation, must not facilitate, for example, progressive viral replication. In a trial in patients with chronic HF (>6 months) with evidence of myocardial inflammation in the absence of continued viral genome persistence, immunosuppressive therapy with cortisone and azathioprine had beneficial effects.[8] The LVEF improved in almost 90% of the treated group versus none in the placebo group and showed a long-term benefit over 20 years.[9] In a long-term (follow-up of 100 months) registry, the authors found that immunosuppressive therapy was associated with better heart transplant-free survival.[10] Unfortunately, further research has not confirmed these positive findings. Mason et al. assigned 111 patients with myocarditis and LV dysfunction to either conventional therapy alone or combined with immunosuppressive therapy with prednisone and either cyclosporin or azathioprine. The primary outcome was the change in LVEF over a 24-week period. This study found that LV function improved regardless of the treatment received and that it did not support the routine treatment of myocarditis with immunosuppressive agents.[11]

Some therapies have been aimed at eliminating the virus in patients without acute myocarditis or myocardial inflammation. Because enterovirus and adenoviruses directly infect the cardiomyocytes, viral clearance with a 6-month course of Interferon beta was associated with an improvement in LVEF and NYHA status.[12] Those with viral clearance had a better survival than those with viral persistence.[13] Unfortunately, to date, randomized trials have not established anti-viral therapy as efficacious for acute myocarditis.[6]

Approaches that have not proven efficacious include intra-venous immunoglobulin[14]; however, this may be effective for certain viral subtypes. Other immunosuppressive

and immunomodulatory approaches are being tested.[6] Anakinra, an interleukin-1 receptor antagonist used in the therapy of connective tissue disorders, has recently been evaluated. Patients with acute myocarditis were randomized within 72 h of the diagnosis to either anakinra or placebo. The endpoints were event-free survival, hospitalization for HF, chest pain requiring medication, LVEF >50%, ventricular arrhythmia, ventricular tachycardia (VT) or ventricular fibrillation (VF). No benefit was seen after 28 days of follow-up.[15]

In summary, there is, as yet, no accepted specific therapy for patients who present with acute myocarditis.

The ARCHER trial is assessing if a pharmaceutically produced cannabidiol formulation, by modulating the immune response in the setting of acute myocarditis, will have beneficial effects in this patient population. We, and others, have demonstrated the significant anti-inflammatory response resulting from the administration of cannabidiol in a number of models of cardiovascular disease. Indeed, a recent study in a model of acute pericarditis has demonstrated that CBD inhibits the development of the NLRP3 inflammasome, a mechanism of inflammation that is important in both the cardiovascular and neurologic systems.[16,17]

Trial design and methods

The ARCHER trial is a phase 2 international, multicentre, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the effects of a pharmaceutically produced cannabidiol formulation (CardiolRx™, Cardiol Therapeutics Inc., Canada) on CMR parameters of LV function and tissue composition in patients with mild to moderate acute myocarditis.

The study design is shown in *Figure* 1.

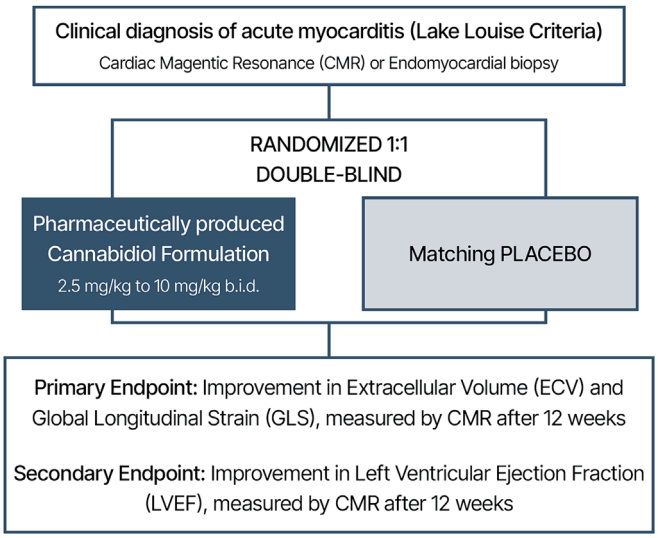
The study was designed in accordance with the Declaration of Helsinki, International Council for Harmonization (ICH), Good Clinical Practice (GCP) guidelines, and all relevant country-specific regulations. The conduct of the study was approved by an institutional review board for each participating centre, and all participants provide written informed consent before any study-related procedures are done. The trial has been registered on ClinicalTrials.gov: NCT05180240.

Patient population

Patients enrolled in the ARCHER study are women and men, ≥18 years of age with mild to moderate acute myocarditis characterized by symptoms of chest pain, arrhythmia, or shortness of breath, often with a history of preceding viral-like illness. Laboratory investigation usually reveals elevated troponin and markers of inflammation (C-reactive protein) plus CMR diagnosis of acute myocarditis (Lake Louise Criteria) within 10 days prior to randomization or endomyocardial biopsy showing either cellular inflammation and/or immunohistochemistry consistent with inflammation.

Key exclusion criteria include presence of coronary artery disease, severe valvular heart disease, inability to undergo CMR assessment, estimated glomerular filtration rate (eGFR) < 30 mL/min, elevated liver function parameters, sepsis, severe left ventricular (LV) dysfunction requiring inotropic support, left ventricular assist device (LVAD) or other circulatory assist devices, or the urgent need for transplantation. In

Figure 1 Trial design.



addition, documented biopsy evidence of giant cell or eosinophilic myocarditis, prior history of sustained ventricular arrhythmia, acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) within the prior 30 days, or a history of QT interval prolongation or having a QTc interval >500 ms are also exclusion criteria.

For a complete list of all eligibility criteria, please refer to *Table* 1.

One hundred patients are being recruited in 38 sites in North America, Brazil, France, and Israel. The first patient was randomized in August 2022.

Study design

Patients with suspected diagnosis of acute myocarditis are consented for a CMR. All CMRs are evaluated centrally by the Imaging Core Laboratory. The Central CMR Laboratory verifies the diagnosis of acute myocarditis according to the Lake Louise criteria and approves the image quality of the outcome parameters before the patient is randomized.

Baseline assessments include a clinical assessment, vital signs and a 12-lead ECG; haematology and blood chemistry, New York Heart Association (NYHA) classification, Columbia Suicide Severity Rating Scale (C-SSRS), and Kansas City Cardiomyopathy Questionnaire (KCCQ). Frozen plasma is retained for central analysis of CBD levels as well as hs-troponin, NT-proBNP, inflammatory markers, and endothelial markers.

Eligible patients are randomized to either cannabidiol or placebo within 10 days of the diagnostic CMR.

Oral study treatment (cannabidiol or placebo) is initiated after randomization and is titrated weekly from 2.5 mg/kg of body weight, to 5.0 and 7.5 to 10 mg/kg body weight b.i.d.

Table 1 Eligibility criteria

Inclusion criteria
1. Males and females 18 years of age or older
2. Diagnosed with acute myocarditis including:
   a. Clinical criteria (symptoms of chest pain, arrhythmia or shortness of breath, or history of viral-like illness), preferably followed by elevated troponin ***PLUS***
   b. CMR diagnosis: (Lake Louise Criteria) within10 days prior to randomization ***OR***
   c. Endomyocardial biopsy showing either cellular inflammation and/or immunohistochemistry consistent with inflammation
3. Male subjects with partners of childbearing potential who have had a vasectomy or are willing to use double barrier contraception methods during the conduct of the study and for 2 months after the last dose of study drug.
4. Women of childbearing potential willing to use an acceptable method of contraception starting with study drug administration and for a minimum of 2 months after study completion. Otherwise, women must be postmenopausal (at least 1 y absence of vaginal bleeding or spotting and confirmed by follicle stimulating hormone [FSH] ≥ 40 mIU/mL [or ≥ 40 IU/L] if <2 years postmenopausal) or be surgically sterile. The following reliable methods of contraception are: parenteral contraceptives, oral contraceptives, patch contraceptives, implantable hormonal contraceptives, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the subject's current practice. Periodic abstinence, that is, calendar, symptothermal, or post-ovulation methods are not an acceptable form of contraception for this study. These methods of contraception also apply to female partners of male subjects.

Exclusion criteria
1. Coronary artery disease (CAD) defined as a stenosis greater than 50% in a major epicardial coronary artery
2. Severe valvular heart disease
3. Inability to safely undergo CMR including administration of gadolinium
4. Estimated glomerular filtration rate (eGFR) < 30 mL/min
5. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) or ALT or AST > 3x ULN plus bilirubin >2x ULN.
6. Sepsis, defined as documented bacteremia at the time of presentation or other documented active infection.
7. Severe left ventricular (LV) dysfunction requiring inotropic support, left ventricular assist device (LVAD) or other circulatory assist devices, or urgent need for transplantation
8. Documented biopsy evidence of giant cell or eosinophilic myocarditis
9. Prior history of sustained ventricular arrhythmia
10. Acute coronary syndrome within 30 days
11. Percutaneous coronary intervention within 30 days
12. History of QT interval prolongation or QTc interval >500 ms
13. Treated with strong inducers CYP3A4 or CYP2C19
14. Treated with digoxin and/or type 1 or 3 antiarrhythmics
15. Current participation in any research study involving investigational drugs or devices
16. Inability or unwillingness to give informed consent
17. Ongoing drug or alcohol abuse
18. Women who are pregnant or breastfeeding
19. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
20. Any factor, which would make it unlikely that the patient can comply with the study procedures
21. On any cannabinoid during the past month
22. Body weight >170 kg
23. Showing suicidal tendency as per the C-SSRS, administered at screening

(or maximally tolerated dose) for a total treatment period of 12 weeks.

During the 12-week treatment period, patients are being re-evaluated seven times for any potential deleterious effect on clinical, ECG or laboratory parameters. Final efficacy assessments are taken place after 12 weeks of study treatment and include a second CMR as well as all other efficacy parameters. A final safety assessment is carried out 1 week after the last dose of study medication.

Standard medications employed for the therapy of the clinical presentation are not altered for the purpose of the study and may include ACE inhibitors, ARBs or ARB/NEP inhibitors, beta-blockers, diuretics, SGLT2 inhibitors, and, if indicated, corticosteroids. The use of cannabinoids, digoxin, type 1 or 3 antiarrhythmics and strong inducers of CYP3A4 and CYP2C19 is not allowed during the study. In addition, drugs that are known to prolong the QT interval must not be started during the trial.

Efficacy assessments

The primary efficacy outcome of the ARCHER trial is comprised of two endpoints, that is, the change in global longitudinal strain (GLS) as a sensitive and re-producible measure of LV function and the change in extracellular volume (ECV) as an estimate of oedema and/or fibrosis, quantified by CMR at 12 weeks post-randomization between the active and the placebo groups.

The secondary efficacy outcome is the difference in the change in LVEF, as measured by CMR, at 12 weeks post-randomization between the two groups.

Exploratory efficacy outcomes include additional CMR parameters, the improvement in other clinical parameters from baseline, such as survival, freedom from major events (cardiac transplant, LVAD, hospitalization for HF) 12 weeks post-randomization, the change in CMR parameters, NYHA classification, Kansas City Cardiomyopathy Questionnaire (KCCQ), as well as hs-troponin, NT-proBNP and inflammatory and endothelial markers from baseline to Week 12. They also include the time to resolution of clinical symptoms, time to normalization of hs-troponin, NT-proBNP and inflammatory and endothelial markers as well as ECG abnormalities.

Safety parameters consist of the number of adverse events (AEs) and serious adverse events (SAEs), changes in ECG parameters, changes in the Columbia Suicide Severity Rating Scale (C-SSRS) as well as changes in laboratory parameters, including liver function parameters, and INR.

Statistical considerations

Sample size calculations were based on published data for GLS and ECV.[18] Assuming 80% power, a 5% alpha risk, and estimated 25% missing CMR follow-up data at Week 12, 100 patients are required to demonstrate the desired treatment effect of 18%.

For both primary outcomes, the means in GLS and ECV at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA procedure, adjusted for baseline means. The two primary outcomes will be considered statistically significant following the Hochberg Procedure[19] in order to preserve the overall type 1 error rate at a level of 0.05 (two-sided).

The same analytical approach will be used to evaluate the effect of study medication on the change in LVEF and other continuous outcomes. Binary outcomes will be compared using a chi-square test. The differences in proportions experiencing these outcomes will be estimated, along with 95% confidence intervals.

The primary analysis population will be the intention-to-treat (ITT) population. Additional sensitivity analyses may be done, if supported by the data.

Discussion

Acute myocarditis imposes a significant burden on patients and is difficult to manage with existing treatment options. No therapies are formally approved by US and European regulatory authorities to treat acute myocarditis.

It is proposed that a pharmaceutically produced cannabidiol formulation, via its anti-inflammatory effects, will favourably modify acute myocarditis, based upon the known anti-inflammatory properties of cannabidiol. Cannabidiol naturally occurs in the *Cannabis sativa* L. plant. However, the cannabidiol used in the pharmaceutically produced cannabidiol formulation is chemically synthesized rather than being extracted from the plant. This provides essentially 100% purity with limits of tetrahydrocannabinol (THC) being below the limit of detection ($<$5 ppm).

Previous experimental data support the potential beneficial effect of cannabidiol in the therapy of acute myocarditis. Cannabidiol has also been shown to reduce oxidative stress, fibrosis, and inflammatory and cell death signalling pathways in models of diabetes,[20] a common co-morbidity in CV disease patients. Cannabidiol has been demonstrated to be protective in the setting of doxorubicin-induced cardiotoxicity, including reducing pro-inflammatory responses in the heart.[21,22]

In a murine model of experimental autoimmune myocarditis (EAM) caused by immunization with the myocarditis inducing cardiac myosin peptide ($\alpha MHC_{334–352}$), treatment with cannabidiol (10 mg/kg, by intraperitoneal administration) reduced infiltration of the myocardium by inflammatory cells, decreased myocardial inflammation as reflected by lowered levels of inflammatory cytokines and chemokines,

and resulted in reduced measures of oxidative stress and a reduction in myocardial fibrosis.[23]

The effect of cannabidiol has also been investigated using the cardiomyoblast cell line H9c2. H9c2 cells display a hypertrophic response to angiotensin II administration, manifested by an increase in surface area of cultured cardiomyocytes. This increase was significantly decreased by cannabidiol. Similarly, the expression of both Brain Natriuretic Peptide (BNP) and collagen by H9c2 cells was significantly increased by angiotensin II and, again, this increase was prevented by cannabidiol (Cardiol Therapeutics, unpublished data). Therefore, in these models, cannabidiol reduces the deleterious effect of angiotensin II on cardiomyocytes, including abrogating increases in cardiomyocyte size and the expression of biomarkers involved in remodelling processes.

In addition, the use of cannabidiol has been tested in the animal model of HF in male C57BL/6 mice, based on the method of Cordero-Reyes.[24] Although not strictly a model of myocarditis, it is a model of cardiac inflammation with associated depression of myocardial function. In this case, subcutaneous administration of cannabidiol reduced inflammation and fibrosis induced by angiotensin-II and was associated with a reduction in cardiomyocyte area. In addition, cannabidiol was associated with reduced expression of BNP in HF hearts (Cardiol Therapeutics, unpublished data). Therefore, in this HF model, cannabidiol administered by subcutaneous injection reduced a number of markers reflecting HF.

Cannabidiol interacts with a range of cellular receptors, which may be involved in the anti-inflammatory activities of cannabidiol. Although cannabidiol has a low binding affinity for the canonical endocannabinoid receptors CB1 and CB2, cannabidiol is active at peroxisome proliferator-activated receptor gamma (PPAR-gamma) receptors, 5-HT1A receptors, adenosine A1 and A2 receptors, transient receptor potential (TRP) channels, including TRPV1, TRPV2, TRPM8, TRPA1, and the G-protein-coupled receptors GPR55, GPR18, GPR6, and GPR3.[25–28]

While the exact mechanism by which cannabidiol exerts its anti-inflammatory effects has not been fully elucidated, current evidence supports its effects on upstream intracellular inflammatory signalling pathways, including inhibiting NLRP3 inflammasome activation, the critical step that leads to downstream interleukin release.[17,28]

In vitro models using activated murine macrophages have demonstrated cannabidiol's ability to significantly decrease the levels of the inflammatory cytokines interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), and significantly inhibit transcription of NLRP3 and pro-IL-1β.[16]

These recent reviews have shown the important role of the NLRP3 inflammasome in the genesis of a number of CV diseases, including myocarditis and acute pericarditis,[29,30] as well as non-CV inflammatory conditions.[31]

In summary, a number of studies have demonstrated that cannabidiol has anti-inflammatory activity in vivo in a range of animal models of both non-CV disorders and CV diseases, including in a murine model of experimental autoimmune myocarditis as well as in in vitro and in vivo models of HF, which are associated with myocardial inflammation and fibrosis. Furthermore, there is evidence of binding of cannabidiol to a range of different receptors, several of which are associated with anti-inflammatory activities. This, plus the demonstration of the inhibitory impact of cannabidiol on the gene transcription of the NLRP3 inflammasome components and substrate Il-1β provides a sound rationale for the ARCHER trial to evaluate the effect of a pharmaceutically produced cannabidiol formulation in patients presenting with acute myocarditis.

Rationale for primary endpoint selection

Changes in LVEF have been traditionally used to assess efficacy of potential therapeutic agents in patients with myocarditis.[8,11,13,14,32] There are several limitations with this approach.[33] First, LVEF does not describe the function of the muscle but rather the change in LV volume over the cardiac cycle. The geometric assumptions used to calculate the end-diastolic and end-systolic volumes are considerable—particularly in patients with segmental wall motion abnormalities. LVEF is also load-dependent, and values can change considerably with changes in preload or afterload and is only moderately reproducible. In some patients with myocarditis the LVEF is markedly depressed and intensive therapy is required to support the circulation. However, in many (perhaps the majority), the LVEF is within the normal range throughout the course of the acute presentation, with the significance of LVEF changes within the normal range being questionable.[34] Because of these limitations, LVEF was selected as the secondary outcome and not one of the primary outcomes.

More recently, there has been renewed interest in estimating LV strain—perhaps as a more sensitive measure of LV function. The development of speckle tracking by echocardiography provided a reproducible means to measure longitudinal, circumferential and radial strain.[35] The same measures are available from CMR images. These studies have revealed that patients presenting with acute myocarditis with normal LVEF measures, have abnormal measures of strain—with longitudinal strain being the most reproducible. Strain measures from CMR images have been shown to have excellent intra- and interobserver reproducibility as well as good interstudy agreement.[36,37] For these reasons, LV GLS was selected as a primary endpoint to enhance the ability to detect changes in myocardial function in response to therapy with a pharmaceutically manufactured cannabidiol formulation.

In addition to impairment of LV function, other characteristic features of acute myocarditis are oedema (secondary to the inflammation) in the early phases of the disease, followed by necrosis and increased fibrosis in the later phases. Both of

these processes expand the ECV in the heart tissue. CMR has been shown to have utility in measuring the ECV in patients with cardiac disease and is particularly helpful in detecting infiltrative diseases, such as amyloidosis or those with increased fibrosis. In patients with acute myocarditis, CMR measures of ECV have revealed more extensive cellular damage than suspected based solely on assessment of the extent of late gadolinium enhancement.[38] ECV has been added as a second primary endpoint to GLS in an attempt to better quantify the abnormal function and structure of the myocardium in this disease.

GLS and ECV have both been found to be independent prognostic predictors of CV outcomes in myocarditis patients.[39,40] Furthermore, change in measures of LV contractility and ECV/oedema between baseline and follow up CMR predict long-term risk for adverse CV outcomes.[41] These findings make GLS and ECV ideal imaging endpoints for this trial as improvements in either or both after 3 months[42] of treatment with a pharmaceutically manufactured cannabidiol formulation compared with placebo would support the potential benefit of this medication in improving clinical outcomes in myocarditis patients.

Conclusions

Currently, there is a significant knowledge gap concerning how acute myocarditis should be treated. To date, few studies have examined therapeutic interventions in the setting of early, acute myocarditis. Most previous studies examining immunosuppressive approaches have examined patients with LV systolic dysfunction and HF in a later phase of the disease process, with mixed results.

The ARCHER trial, in contrast, will study the effect of a pharmaceutically produced cannabidiol formulation in the acute phase of the disease process. The hypothesis, based on the known anti-inflammatory effects of cannabidiol, is that this intervention will modulate the immunomediated inflammatory response with beneficial effects on CMR measures of LV contractility and extracellular volume/oedema. With this approach, the ARCHER trial will potentially begin to fill the gap concerning how patients with acute myocarditis should be treated. If a beneficial effect is observed concerning the endpoints chosen in this phase-II study, a larger study, examining the impact of cannabidiol on clinical outcome variables, will be required to confirm clinical benefit.

Acknowledgements

All CMRs are analysed centrally by the Imaging Core Laboratory at McGill University, Montreal, Canada. SOCAR Research SA., Nyon, Switzerland, is responsible for the overall data management and management of local Contract Research Organizations. TMC Pharma, Hants, United Kingdom, is responsible for pharmacovigilance. We would like to thank all patients, the study coordinators, the investigators and all the investigative site personnel for their participation in the trial.

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

AB: research grant and scientific advisory committee for Cardiol Therapeutics Inc., LTC: scientific advisory committee for Cardiol Therapeutics Inc. MGWF: institution receives research funding from Cardiol Therapeutics Inc. GT: institution receives research funding from Cardiol Therapeutics Inc., receives payment as director of Cardiol Therapeutics Inc, ABP: employee of Cardiol Therapeutics Inc. ERS: consultant and shareholder of Cardiol Therapeutics Inc. With the exception of ABP, ERS and GT, all authors received payment from Cardiol Therapeutics Inc. for service on the trial steering committee.

Funding

This trial is sponsored by Cardiol Therapeutics Inc., Canada; no additional funding was used to support this manuscript.

References

1. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, *et al*. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2020;**12**:169-193. doi:10.1038/s41569-020-00435-x
2. Matsumori A, Furukawa Y, Hasegawa K, Sato Y, Nakagawa H, Morikawa Y, *et al*. Epidemiologic and clinical characteristics of cardiomyopathies in Japan: results from nationwide surveys. *Circ J Off J Jpn Circ Soc* 2002;**66**:323-336. doi:10.1253/circj.66.323
3. Fairweather D, Beetler DJ, Di Florio DN, Musigk N, Heidecker B, Cooper LT. COVID-19, myocarditis and pericarditis. *Circ Res* 2023;**132**:1302-1319. doi:10.1161/CIRCRESAHA.123.321878
4. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM,

et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;**71**:1755-1764. doi:10.1016/j.jacc.2018.02.037
5. Sagar S, Liu PP, Cooper LT. Myocarditis. *Lancet Lond Engl* 2012;**379**:738-747. doi:10.1016/S0140-6736(11)60648-X
6. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res* 2019;**124**:1568-1583. doi:10.1161/CIRCRESAHA.118.313578
7. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, *et al*. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. *Circulation* 2017;**136**:529-545. doi:10.1161/CIRCULATIONAHA.117.026386
8. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009;**30**:1995-2002. doi:10.1093/eurheartj/ehp249
9. Chimenti C, Russo MA, Frustaci A. Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy: 20-year follow-up of the TIMIC trial. *Eur Heart J* 2022;**43**:3463-3473. doi:10.1093/eurheartj/ehac348
10. Merken J, Hazebroek M, Van Paassen P, *et al*. Immunosuppressive therapy improves both short- and long-term prognosis in patients with virus-negative nonfulminant inflammatory cardiomyopathy. *Circ Heart Fail* 2018;**11**:e004228. doi:10.1161/CIRCHEARTFAILURE.117.004228
11. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, *et al*. A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. *N Engl J Med* 1995;**333**:269-275. doi:10.1056/NEJM199508033330501
12. Kühl U, Pauschinger M, Schwimmbeck PL, *et al*. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation* 2003;**107**:2793-2798. doi:10.1161/01.CIR.0000072766.67150.51
13. Kühl U, Lassner D, von Schlippenbach J, Poller W, Schultheiss HP. Interferon-Beta improves survival in enterovirus-associated cardiomyopathy. *J Am Coll Cardiol* 2012;**60**:1295-1296. doi:10.1016/j.jacc.2012.06.026
14. McNamara DM, Holubkov R, Starling RC, *et al*. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation* 2001;**103**:2254-2259. doi:10.1161/01.cir.103.18.2254
15. Kerneis M, Cohen F, Combes A, Vicaut E, Montalescot G. The ARAMIS trial. Anakinra versus placebo, a double blind randomized controlled trial for the treatment of acute myocarditis. Presented at: ESC Congress; Amsterdam, 2023.
16. Martinez Naya N, Nirar AH, Kim MM, *et al*. Protective effects of cannabidiol in a mouse model of acute pericarditis. *Circ Res* 2022;**131**:e169-e190. doi:10.1161/RES.0000000000000584
17. Martinez Naya N, Kelly J, Corna G, Golino M, Polizio AH, Abbate A, *et al*. An overview of cannabidiol as a multifunctional drug: pharmacokinetics and cellular effects. *Mol Basel Switz* 2024;**29**:473. doi:10.3390/molecules29020473
18. Isaak A, Kravchenko D, Mesropyan N, Endler C, Bischoff LM, Vollbrecht T, *et al*. Layer-specific strain analysis with cardiac MRI feature tracking in acute myocarditis. *Radiol Cardiothorac Imaging* 2022;**4**:e210318. doi:10.1148/ryct.210318
19. Benjamini Y, Hochberg Y. Controlling the false discovery rate:a practical and powerful approach to multiple testing. *J R Stat Soc* 1995;**57**:289-300.
20. Rajesh M, Mukhopadhyay P, Bátkai S, Patel V, Saito K, Matsumoto S, *et al*. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:2115-2125. doi:10.1016/j.jacc.2010.07.033
21. Fouad AA, Albuali WH, Al-Mulhim AS, Jresat I. Cardioprotective effect of cannabidiol in rats exposed to doxorubicin toxicity. *Environ Toxicol Pharmacol* 2013;**36**:347-357. doi:10.1016/j.etap.2013.04.018
22. Hao E, Mukhopadhyay P, Cao Z, Erdélyi K, Holovac E, Liaudet L, *et al*. Cannabidiol protects against doxorubicin-induced cardiomyopathy by modulating mitochondrial function and biogenesis. *Mol Med* 2015;**21**:38-45. doi:10.2119/molmed.2014.00261
23. Lee WS, Erdelyi K, Matyas C, Mukhopadhyay P, Varga ZV, Liaudet L, *et al*. Cannabidiol limits T cell-mediated chronic autoimmune myocarditis: implications to autoimmune disorders and organ transplantation. *Mol Med* 2016;**22**:136-146. doi:10.2119/molmed.2016.00007
24. Cordero-Reyes AM, Youker KA, Trevino AR, Celis R, Hamilton DJ, Flores-Arredondo JH, *et al*. Full expression of cardiomyopathy is partly dependent on B-cells: a pathway that involves cytokine activation, immunoglobulin deposition, and activation of apoptosis. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis* 2016;**5**: doi:10.1161/JAHA.115.002484
25. Brown AJ. Novel cannabinoid receptors. *Br J Pharmacol* 2007;**152**:567-575. doi:10.1038/sj.bjp.0707481
26. Laun AS, Song ZH. GPR3 and GPR6, novel molecular targets for cannabidiol. *Biochem Biophys Res Commun* 2017;**490**:17-21. doi:10.1016/j.bbrc.2017.05.165
27. Morales P, Reggio PH. An update on non-CB1, non-CB2 cannabinoid related G-protein-coupled receptors. *Cannabis Cannabinoid Res* 2017;**2**:265-273. doi:10.1089/can.2017.0036
28. Martinez Naya N, Kelly J, Corna G, Golino M, Abbate A, Toldo S. Molecular and cellular mechanisms of action of cannabidiol. *Mol Basel Switz* 2023;**28**:5980. doi:10.3390/molecules28165980
29. Toldo S, Mezzaroma E, Buckley LF, Potere N, di Nisio M, Biondi-Zoccai G, *et al*. Targeting the NLRP3 inflammasome in cardiovascular diseases. *Pharmacol Ther* 2022;**236**:108053. doi:10.1016/j.pharmthera.2021.108053
30. Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. *Nat Rev Cardiol* 2024;**21**:219-237. doi:10.1038/s41569-023-00946-3
31. Chu FX, Wang X, Li B, Xu LL, Di B. The NLRP3 inflammasome: a vital player in inflammation and mediating the anti-inflammatory effect of CBD. *Inflamm Res Off J Eur Histamine Res Soc Al* 2024;**73**:227-242. doi:10.1007/s00011-023-01831-y
32. Cavalli G, Pappalardo F, Mangieri A, Dinarello CA, Dagna L, Tresoldi M. Treating life-threatening myocarditis by blocking Interleukin-1. *Crit Care Med* 2016;**44**:e751-e754. doi:10.1097/CCM.0000000000001654
33. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J* 2016;**37**:1642-1650. doi:10.1093/eurheartj/ehv510
34. André F, Stock FT, Riffel J, Giannitsis E, Steen H, Scharhag J, *et al*. Incremental value of cardiac deformation analysis in acute myocarditis: a cardiovascular magnetic resonance imaging study. *Int J Cardiovasc Imaging* 2016;**32**:1093-1101. doi:10.1007/s10554-016-0878-0
35. Hsiao JF, Koshino Y, Bonnichsen CR, Yu Y, Miller FA Jr, Pellikka PA, *et al*. Speckle tracking echocardiography in acute myocarditis. *Int J Cardiovasc Imaging* 2013;**29**:275-284. doi:10.1007/s10554-012-0085-6
36. Taylor RJ, Moody WE, Umar F, Edwards NC, Taylor TJ, Stegemann B, *et al*. Myocardial strain measurement with feature-tracking cardiovascular magnetic resonance: normal values. *Eur Heart J Cardiovasc Imaging* 2015;**16**:871-881. doi:10.1093/ehjci/jev006
37. Andre F, Steen H, Matheis P, Westkott M, Breuninger K, Sander Y, *et al*. Age- and gender-related normal left ventricular deformation assessed by cardiovascular magnetic resonance feature tracking. *J Cardiovasc Magn Reson* 2015;**17**:25. doi:10.1186/s12968-015-0123-3
38. Radunski UK, Lund GK, Säring D, Bohnen S, Stehning C, Schnackenburg B, *et al*. T1 and T2 mapping cardiovascular magnetic resonance imaging techniques reveal unapparent myocardial injury in patients with myocarditis. *Clin Res Cardiol* 2017;**106**:10-17. doi:10.1007/s00392-016-1018-5

39. Gräni C, Bière L, Eichhorn C, Kaneko K, Agarwal V, Aghayev A, *et al*. Incremental value of extracellular volume assessment by cardiovascular magnetic resonance imaging in risk stratifying patients with suspected myocarditis. *Int J Cardiovasc Imaging* 2019;**35**:1067-1078. doi:10.1007/s10554-019-01552-6
40. Fischer K, Obrist SJ, Erne SA, Stark AW, Marggraf M, Kaneko K, *et al*. Feature tracking myocardial strain incrementally improves prognostication in myocarditis beyond traditional CMR imaging features. *JACC Cardiovasc Imaging* 2020; **13**:1891-1901. doi:10.1016/j.jcmg.2020.04.025
41. Soeiro AM, Bossa AS, César MC, Leal TCAT, Garcia G, Fonseca RA, *et al*. The association of myocardial strain with cardiac magnetic resonance and clinical outcomes in patients with acute myocarditis. *Front Cardiovasc Med* 2023;**10**:1121083. doi:10.3389/fcvm.2023.1121083
42. Berg J, Kottwitz J, Baltensperger N, Kissel CK, Lovrinovic M, Mehra T, *et al*. Cardiac magnetic resonance imaging in myocarditis reveals persistent disease activity despite normalization of cardiac enzymes and inflammatory parameters at 3-month follow-up. *Circ Heart Fail* 2017;**10**:e004262. doi:10.1161/CIRCHEARTFAILURE.117.004262