ESC European Society of Cardiology

ESC Heart Failure (2026) **13**, xvag058
https://doi.org/10.1093/eschf/xvag058

STUDY DESIGN

Colchicine in patients with chronic inflammatory cardiomyopathy: rationale and design of the CMP-MYTHiC

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Received 7 September 2025; revised 29 November 2025; accepted 13 February 2026; online publish-ahead-of-print 24 February 2026

Abstract

Introduction Acute myocarditis can lead to chronic inflammatory cardiomyopathy (Infl-CMP), a condition characterized by increased risk of ventricular arrhythmias (VA), left ventricular (LV) systolic dysfunction (LVSD), and heart failure (HF). Immunosuppressive

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therapy is generally not recommended for Infl-CMP when diagnosed non-invasively by cardiac magnetic resonance imaging (CMRI) or fluorodeoxyglucose-positron emission tomography (FDG-PET). We are assessing, in the CMP-MYTHiC trial, whether colchicine (0.5 mg in patients <70 kg or 1 mg in patients ≥70 kg), an immunomodulatory drug with a good safety profile, can reduce myocardial inflammation in patients with Infl-CMP.

Study design The CMP-MYTHiC, a multicenter investigator-initiated single-blinded randomized controlled trial, screens adult patients diagnosed with Infl-CMP by CMRI or FDG-PET within the prior 3 months at 12 Italian centres. Eligibility is further defined by the presence of VA or LVSD/HF phenotype. VA phenotype is determined by a high burden of premature ventricular complexes (PVCs) on baseline 24-h ECG ambulatory monitoring, non-sustained ventricular tachycardia (NSVT), or sustained ventricular tachycardia (SVT). The LVSD/HF phenotype is characterized by reduced LV ejection fraction (LVEF <50% on echocardiogram or <60% on CMRI) or elevated natriuretic peptide levels. Key exclusion criteria include a history of myocardial infarction, cardiomyopathy attributed to other specific causes, and systemic autoimmune disorders.

The efficacy of colchicine compared with placebo will be assessed when CMRI or FDG-PET scans and 24-h ambulatory ECG monitoring are repeated at 6 months after randomization. The primary endpoint of the trial analysed according to the intention-to-treat population is the proportion of patients who are alive and free from any clinical (cardiac death or hospitalization due to HF or VA episodes), arrhythmic (PVC burden increase ≥50%, NSVT increase ≥30%, or any SVT), or imaging (LVEF reduction >10% or new areas of oedema plus increased inflammation) worsening, and who demonstrate improvement in either imaging (reduction in oedema on CMRI or FDG uptake) or arrhythmic (PVC burden reduction ≥70% with no NSVT/SVT) outcomes at 6 months. Assuming 80% power with an overall type I error of 0.025 using one-sided Fisher's Exact test, 40 patients per group are required to demonstrate that the primary endpoint will be reached in 66% of patients in the colchicine group compared with 33% in the placebo. Twenty-nine patients were randomized since December 2023, and the conclusion is expected in 2029.

Discussion The results can define the role of colchicine in treating patients with Infl-CMP non-invasively diagnosed by CMRI or FDG-PET.

Clinicaltrials.gov identifier NCT06158698.

Keywords Colchicine • Myocarditis • Inflammatory cardiomyopathy • Randomized clinical trial • Ventricular arrhythmias • Cardiac magnetic resonance imaging

Introduction

Myocarditis is an inflammatory condition that affects the myocardium, primarily triggered by viral infections or autoimmune disorders.[1–4] In a subset of patients, myocarditis may progress to chronic inflammatory cardiomyopathy (Infl-CMP), characterized by an increased risk of ventricular arrhythmias (VA), left ventricular (LV) systolic dysfunction (LVSD), and heart failure (HF).[5] Most patients with Infl-CMP are diagnosed non-invasively with cardiac magnetic resonance imaging (CMRI) or, less frequently, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans.[1,2,6] Endomyocardial biopsy (EMB) is an invasive diagnostic tool with high specificity but low sensitivity.[7] EMB is underutilized despite its recognized utility;[8] thus, in most patients, the diagnosis of Infl-CMP relies on imaging, especially in patients with milder forms.[1] No specific immunosuppressive treatments are recommended for patients with chronic Infl-CMP with LVSD/HF or VA phenotype and evidence of inflammation on imaging.[1,6,9,10] Only one trial demonstrated the efficacy of prednisone plus azathioprine in patients with chronic HF, reduced LV ejection fraction (EF), and histological evidence of lymphocytic myocarditis (TIMIC trial).[11] Furthermore, for specific myocarditis histopathological subtypes, such as giant cell myocarditis, sarcoidosis, eosinophilic myocarditis, or myocarditis associated with systemic inflammatory disorders, there is consensus that immunosuppressive agents are effective, with corticosteroids as first-line therapy in most cases.[1,5,6,12,13] The identification of myopathic cardiac gene variants (MCGVs), such as those associated with dilated or arrhythmogenic cardiomyopathies, in 8–31% of patients with myocarditis, has made the scenario of specific treatments for Infl-CMP even more complex.[14–19] Desmoplakin gene (*DSP*) pathogenic (P) or likely pathogenic (LP) variants have been mainly observed among patients with myocarditis and near-normal LVEF who are at increased risk of VA or recurrent episodes of myocarditis and who can develop an arrhythmogenic CMP phenotype.[18] In contrast, titin gene truncating variants have been mainly observed in patients with a dilated cardiomyopathy phenotype characterized by LVSD and HF.[16,17,19] With easier access to genetic testing, a significant overlap between inflammatory and inherited cardiomyopathies has been increasingly observed.[14,20] This genetic susceptibility, in combination with secondary triggers such as viral infections or mechanical stress, may provoke recurrent episodes leading to chronic Infl-CMP.[15,17,21,22] Thus, it must be demonstrated that in this specific subset of patients, immunomodulating drugs can prevent recurrent inflammatory myocardial injuries and progression towards more severe forms of Infl-CMP. To date, immunosuppressive therapy is not universally recommended in genetically associated Infl-CMP, despite an increasing number of case reports suggesting the effectiveness of different immunosuppressive agents in these patients, especially during acute episodes.[23–26] In a recent retrospective registry of patients with P/LP DSP cardiomyopathy presenting with myocarditis or recurrent myocarditis, immunosuppressive agents improved the long-term outcome of these patients, further supporting a potential role for immunosuppression in patients with non-invasively diagnosed Infl-CMP and a genetic background.[27] Another registry (MAVERIC registry),[28] including 55 symptomatic patients with >5000 premature ventricular complexes (PVCs)/24 h on ECG Holter ambulatory monitoring and FDG-PET imaging consistent with Infl-CMP, showed that a signal of benefit was observed in patients who received prednisone 40 mg for

3 months.[28] The benefit was defined as a reduction in the PVC burden by >80% and a negative FDG-PET scan at follow-up.[28] Similar results were observed in another registry, where 116 patients with myocarditis identified by EMB and VA were studied. Those treated with immunosuppressive agents showed a significant reduction in minor VA burden, as well as improvement in clinical, laboratory, and imaging findings, compared with those who did not receive immunosuppressive treatment.[29] Unfortunately, long-term treatment with high-dose corticosteroids, as in the TIMIC trial and the MAVERIC registry (>10 mg prednisone for >1 month), is associated with comorbidities such as a higher risk of arterial hypertension, diabetes, hyperglycaemia, weight gain, infections, and osteoporosis. Based on these premises, there is a strong rationale for pilot trials to identify immunosuppressive drugs that can reduce myocardial inflammation and improve clinical outcomes. Colchicine, an immunomodulatory drug with a favourable safety profile and beneficial effects in patients with pericarditis and coronary artery disease, may decrease myocardial inflammation in these patients, without significant risks.[30–34] In a registry of 175 patients with pericarditis associated with myocardial involvement, there was a more prolonged event-free survival among those taking colchicine, with only 1.7% experiencing a colchicine-associated side effect.[35] In addition, a US administrative analysis of 1137 patients treated with colchicine versus a matched cohort of 1137 patients not treated with colchicine showed a lower risk of 90-day incidence of the composite outcome of all-cause death, VA, and acute HF from 17.0% in the colchicine group to 24.5% in the group without colchicine ($P < .001$).[36] Furthermore, *in vitro* experiments using engineered heart tissues with human-induced pluripotent stem cell-derived cardiomyocytes from patients with heterozygous DSP showed that colchicine improved the strain-induced force deficits,[30] providing a rationale for testing colchicine also in patients with Infl-CMP and a genetic background. The CMP-MYTHiC trial aims to determine whether colchicine, compared with placebo, can reduce myocardial inflammation and improve clinical outcomes in patients with Infl-CMP. Both MCGV-positive and MCGV-negative patients will be randomized in the trial to assess whether genetic background influences response to colchicine. By investigating colchicine as an adjunct to optimized medical therapy (OMT), CMP-MYTHiC aims to identify a new therapeutic option for safely reducing myocardial inflammation. Compared with previous trials and registries, the novelty here is the first use of colchicine in the setting of Infl-CMP. A companion CMP-MYTHiC registry will be conducted in parallel.

Trial design and methods

Study overview

The CMP-MYTHiC trial is a single-blinded, investigator-initiated, multicentre, phase III randomized controlled study with a 6-month intervention period designed to evaluate the immunomodulatory effects of colchicine compared with placebo in reducing myocardial inflammation or ventricular arrhythmic burden after 6 months in patients with chronic Infl-CMP diagnosed by non-invasive imaging. The duration of the intervention period will be 6 months, with the primary endpoint of the trial assessed after 6 months when the follow-up CMRI or FDG-PET scan and the 24-h ECG ambulatory monitoring will be available. An extension of the clinical follow-up to 2 years has been planned.

The trial is conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. Approval was obtained at the Italian (initial approval by the Agenzia Italiana del Farmaco with the EudraCT identifier 2022-003912-99 on 26 April 2023) and European levels [approved transition by the European Medicines Agency (EMA) with the EU-CT number: 2024-5179451400 on 28 October 2024], as well as from institutional review boards at each participating centre (approval from Comitato Etico Milano Area 3 on date 11 May 2023 for the coordinating centre ASST Grande Ospedale Metropolitano Niguarda in Milano, Italy). All participants provided written informed consent before any study-related procedures were initiated. The trial is registered on ClinicalTrials.gov (NCT06158698; first version on record 28 November 2023). The first patient was randomized on 21 December 2023, and 29 patients have been randomized to date, representing 33.8% of the planned total. Compared with the planned end of the trial in 2026, an extension to 2029 has been submitted to EMA. Protocol version 3.0, dated 27 April 2023, was applied during the randomization of these patients, and a new amendment is planned for submission to the EMA, with minor changes that will be presented in this manuscript.

Patient population

Patients enrolled in the CMP-MYTHiC trial are adult men and women (aged 18 years or older), non-invasively diagnosed with Infl-CMP by CMRI or FDG-PET scan performed in the 3 months before randomization. Histologic diagnosis of myocarditis without proven evidence of inflammation on CMRI or FDG-PET is not considered sufficient to be included in the trial, because quantification of changes at baseline and after 6 months would not be possible without repetition of EMB, and in any case, not comparable to changes detected by imaging that occur on the whole myocardium. Eligibility is further defined by the presence for at least 1 month since the initiation of symptoms of at least one of following characteristics: (i) high burden of PVCs on 24-h ECG ambulatory monitoring (≥3000 PVCs/24 h), or presence of non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (SVT), (ii) reduced LVEF (<50% on echocardiogram or <60% on CMRI), (iii) increased levels of natriuretic peptides (NT-proBNP ≥ 1000 pg/mL or BNP ≥ 200 pg/mL), (iv) elevated levels of high-sensitivity troponin above the upper reference limit after 2 months from the initial assessment in combination with ≥1000 PVCs/24 h on 24-h ECG ambulatory monitoring. In the new amendment, planned in 2026, the PVC threshold for inclusion was reduced to ≥500/24 h, independently of troponin levels, based on recent evidence presented in the discussion. Key exclusion criteria include history of myocardial infarction with evidence of scar, significant residual flow-limiting coronary artery disease, cardiomyopathy attributed to other specific causes, previous cardiac surgery, chronic infective diseases such as HIV or tuberculosis, symptomatic atrial arrhythmias, expected life expectancy <12 months, known systemic autoimmune disorders where immunosuppression may be beneficial or ongoing chronic immunosuppressive therapies, hypereosinophilic syndromes, advanced HF (NYHA class III-IV or need for inotropes), potential contraindication to colchicine (i.e. allergies to the medication or excipients, renal insufficiency, hepatic cirrhosis or elevated transaminase, or severe gastrointestinal insufficiency). Women of childbearing potential and those breastfeeding are excluded due to insufficient data on the embryo-foetal risks associated with colchicine, or those participants involved in another trial. The detailed and complete list of exclusion criteria is presented in *Figure 1*.

Study design

The planned sample size is 80 patients (40 per group: interventional and placebo), recruited across 10 centres in Italy, based on the statistical plan presented in the Statistical Considerations section. In the new amendment, two more Italian centres will be included. The complete list of Italian centres and the names of the local principal investigators is available in the Supplementary Table S1. Patients diagnosed non-invasively with Infl-CMP based on CMRI criteria following the 2018 Lake Louise criteria, or FDG-PET based on FDG myocardial uptake, will be screened (*Figure 2*).[37] The patients will be included if inflammation is associated with VA burden as previously described, LVSD, or signs of HF that include mild signs of systolic function impairment

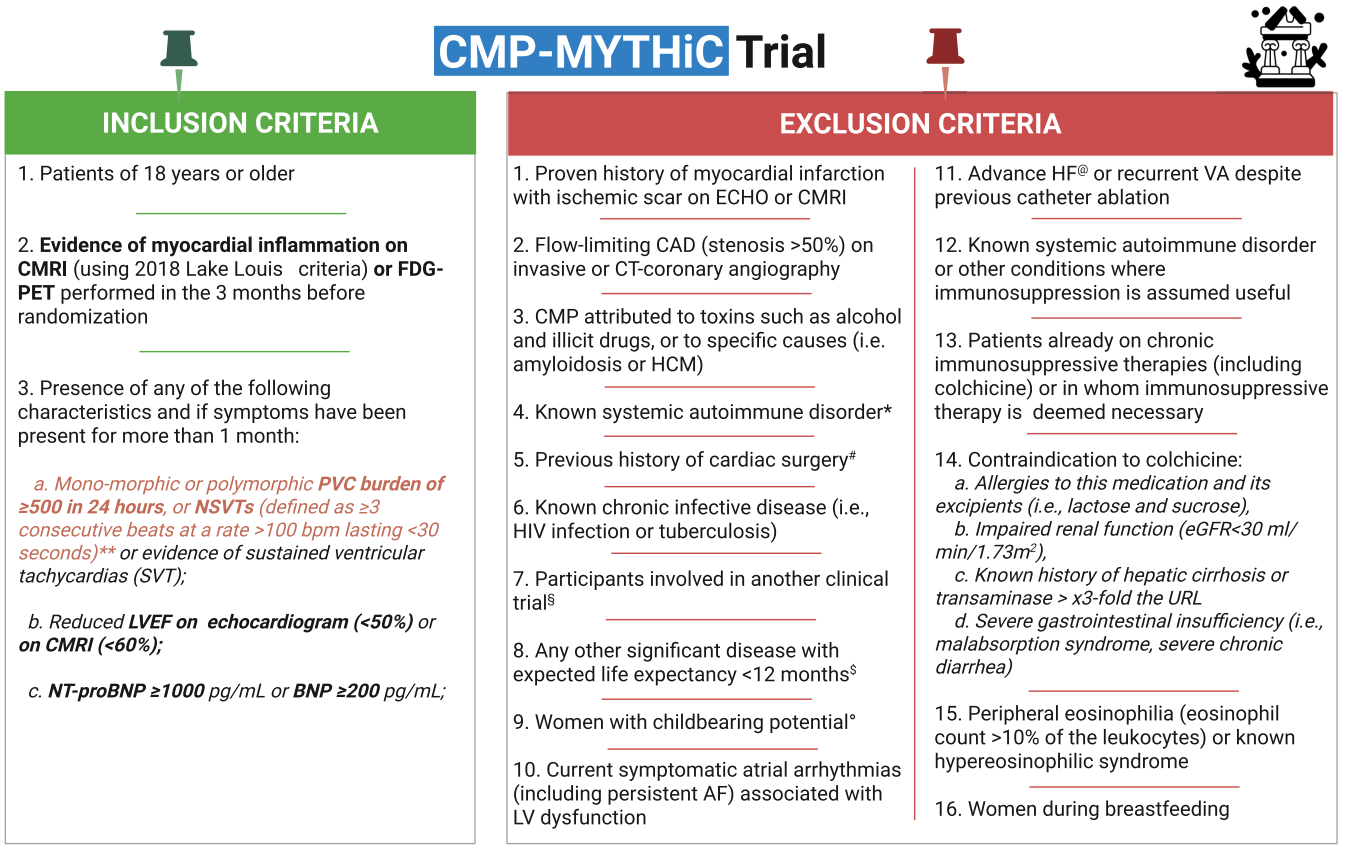

Figure 1 Inclusion and exclusion criteria of the CMP-MYTHiC trial. *The exception will be for patients with systemic autoimmune disease or isolated cardiac sarcoidosis with a family history of cardiomyopathy, myocarditis, or arrhythmias, where overlap between an autoimmune event and a genetic background can occur. These patients will undergo genetic tests. Patients with autoimmune systemic disorders and isolated cardiac sarcoidosis with positive genetic tests for myopathic cardiac gene variants will be included in the registry. #History of cardiac surgery, for instance, §Participation in a clinical trial in which an investigational drug was administered in the 30 days before screening, or five half-lives of the study drug, whichever is longer. $Significant disease or disorder which may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial in the opinion of the Investigator. °This exclusion criterion is due to insufficient human information regarding the embryo-foetal risk with colchicine. @NYHA III or need for inotropes, including levosimendan. **In the ongoing request for an amendment, a change regarding the definition of NSVT has been included to be aligned with the current definition of NSTV. In fact, we modified from 'defined as >3 consecutive beats lasting <30 seconds' to 'defined as ≥3 consecutive beats at a rate >100 beats per minute lasting <30 seconds.' In addition, the new amendment reduced the PVC threshold for inclusion to ≥500/24 h, independent of troponin levels. This inclusion criterion replaces the following inclusion criteria: (i) high burden of PVCs on 24-h ECG ambulatory monitoring (≥3000 PVCs/24 h), or presence of non-sustained ventricular tachycardia, sustained ventricular tachycardia, (ii) elevated levels of high-sensitivity troponin above the upper reference limit after 2 months from the initial assessment in combination with ≥1000 PVCs/24 h on 24-h ECG ambulatory monitoring. To mark this change, the proposed new inclusion criterion is in red in the figure. BNP indicates B-type natriuretic peptide; CAD, coronary artery disease; CMP, cardiomyopathy; CMRI, cardiac magnetic resonance imaging; ECHO, echocardiographic exam; eGFR, estimated glomerular renal filtration; HCM, hypertrophic cardiomyopathy; FDG-PET, fluorodeoxyglucose-positron emission tomography; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MCGV, myopathic cardiac gene variants; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PVC, premature ventricular complex; SVT, sustained ventricular tachycardia, URL, upper reference limit; VA, ventricular arrhythmias

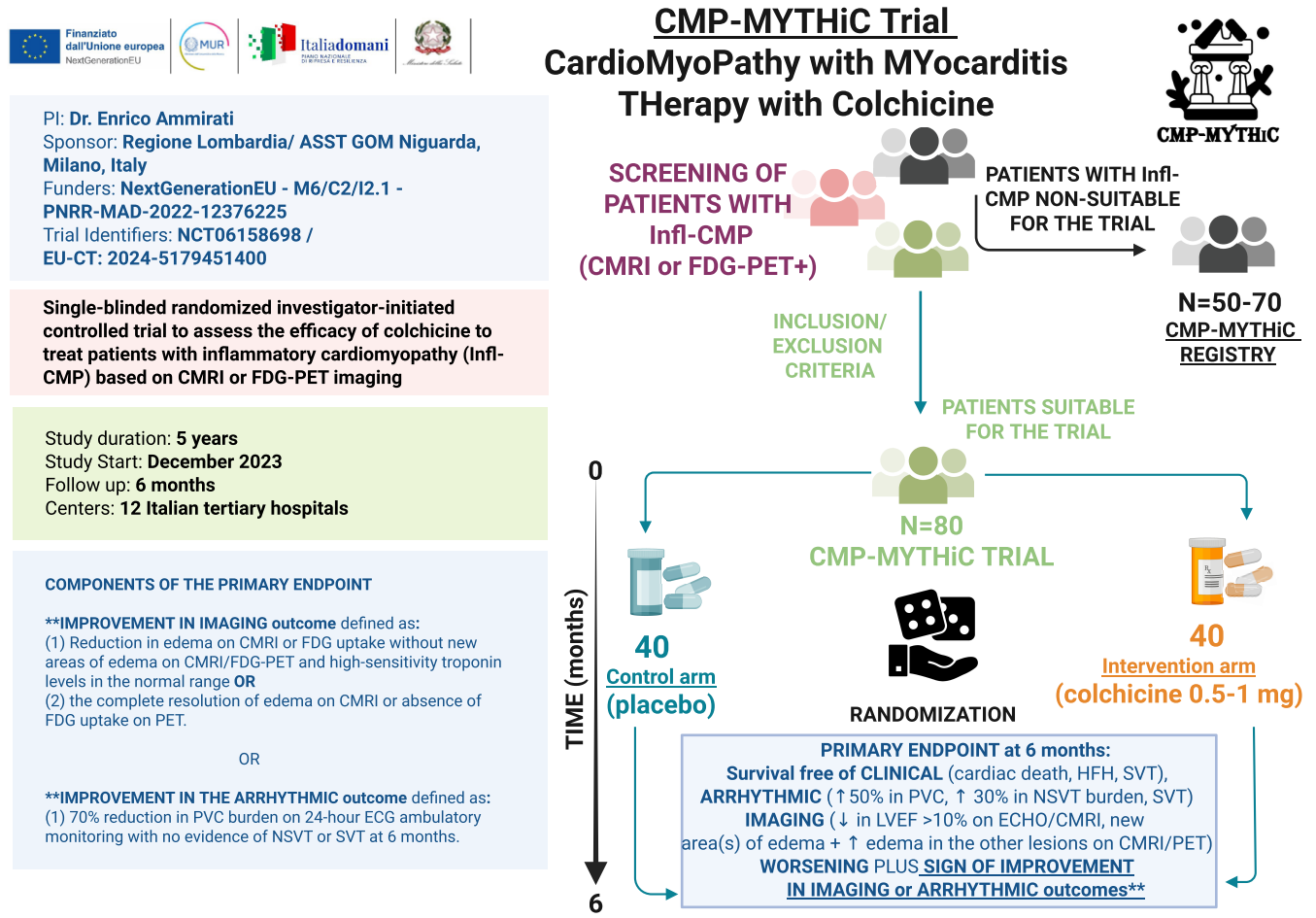

Figure 2 Flow chart of the CMP-MYTHiC trial. CMP, cardiomyopathy; CMRI, cardiac magnetic resonance imaging; ECHO, echocardiographic exam; FDG-PET, fluorodeoxyglucose-positron emission tomography; HFH, hospitalization due to heart failure; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; and SVT, sustained ventricular tachycardia. In the trial, patients will be included if a non-invasive diagnosed of Infl-CMP by CMRI or FDG-PET is reached within 3 months before inclusion in the registry. Created in BioRender. Ammirati, E. (2026) https://BioRender.com/fvwaefy

(LVEF < 50% on echocardiogram or <60% on CMRI), or elevated natriuretic peptides. Furthermore, these patients will be enrolled if they meet the exclusion criteria (*Figure 1*). Those patients with evidence of Infl-CMP and the presence of exclusion criteria (i.e. current assumption of corticosteroids) not associated with a systemic autoimmune disorder will be included in a prospective companion registry termed the CMP-MYTHiC registry. Full description of the inclusion and exclusion criteria in the CMP-MYTHiC registry is presented in the Supplementary Figure S1. In particular, the registry will not exclude women with childbearing potential, patients with symptomatic atrial fibrillation, advanced HF (NYHA III or need for inotropes including levosimendan), or recurrent VA despite previous catheter ablation, patients already on chronic immunosuppressive therapies (including colchicine), or contraindications to the assumption of colchicine. In the registry, patients will be included if a non-invasive diagnosis of Infl-CMP by CMRI or FDG-PET is established within 12 months before inclusion. Enrolment may occur during hospital admission or in outpatient clinics in patients with signs or symptoms attributable to the Infl-CMP lasting for at least 1 month, avoiding cases of first acute myocarditis with cardiac onset within 1 month.[1,6] Baseline assessments include a clinical evaluation, 12-lead ECG, blood tests including troponin and natriuretic peptides, echocardiography, New York Heart Association (NYHA) classification, the EuroQoL 5-Dimension (EQ-5D) quality of life questionnaire, and the Kansas City Cardiomyopathy Questionnaire (KCCQ). While a list of core variables is provided for data collection, the trial adopts a pragmatic approach, avoiding additional tests that are not part of standard practice at the participating centres. The variables included in the primary and secondary endpoints align with standard care protocols in Italian centres. A CMRI or FDG-PET scan and a 24-hour ECG Holter monitor performed within the last 3 months before randomization must be available and used as a baseline to assess imaging and arrhythmic outcomes 6 months after the initial randomization. Genetic testing may be performed after randomization, if it has not already been done, due to emerging evidence that a significant proportion of Infl-CMP of unknown aetiology may have a genetic background that can impact risk management for these patients.[14,17] Among patients recruited in the trial or the registry who sign a specific informed consent, blood samples will also be collected for *ex vivo* analyses. Primary and secondary endpoints, including baseline and follow-up echocardiographic, CMRI, and FDG-PET findings, will be centrally analysed by investigators who are blinded to treatment allocation at Niguarda Hospital in Milano, Italy (the trial sponsor). Furthermore, clinicians involved in imaging analysis will not directly manage patients who are enrolled in the trial. Eligible patients will be randomized 1:1 to receive either colchicine (0.5–1 mg) or placebo, on top of OMT, within 3 months of the diagnostic CMRI or PET imaging. The oral study treatment is initiated following randomization, starting with a dose of 0.5 mg for 2 weeks. The dosage may then be increased to 1 mg daily in patients weighing ≥70 kg. In this way, we expect greater tolerance to treatment and a reduced risk of diarrhoea. In case of intolerance with colchicine 1 mg in patients ≥70 kg, such as nausea or diarrhoea, they may return to the initial dose of 0.5 mg once daily. During the treatment period, follow-up patient contacts are scheduled at 3 months (remote or outpatient) to assess clinical status and at 6 months to evaluate the primary efficacy endpoint. The 6-month follow-up includes imaging with CMRI (in particular to determine the presence of oedema based on STIR sequences or T2 mapping, LVEF) and/or FDG-PET (to evaluate FDG update as a marker of myocardial inflammation), as well as re-evaluation with 24-h ECG monitoring, blood tests, echocardiography, and health assessment questionnaires (i.e. EuroQoL-5D [EQ-5D] and KCCQ). The study does not mandate specific visits during this period, although they are expected based on the patients' clinical condition. While the trial will assess the primary and secondary endpoints at 6 months, an extension up to 2 years of follow-up without additional assumption of colchicine. Standard OMT are not altered for the study. They may include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or angiotensin receptor neprilysin inhibitor, beta-blockers, diuretics, sodium-glucose cotransporter 2 inhibitors, vericiguat, and, if indicated, amiodarone or other antiarrhythmic medications.

Efficacy assessment

The primary objective is to assess the efficacy of colchicine compared with placebo. It is expected that, among patients on colchicine plus OMT, a larger proportion will reach the primary efficacy endpoint than in the placebo plus OMT arm. For all other secondary endpoints, the aim is to assess the superiority of colchicine vs placebo on top of OMT. The primary endpoint of the CMP-MYTHiC trial is the proportion of patients alive and free from clinical worsening, arrhythmic burden, or adverse imaging outcomes, and who demonstrate at least one sign of improvement in imaging or arrhythmic outcomes at 6 months post-randomization (*Figure 2*).

Clinical worsening is defined as the occurrence of at least one of the following: cardiac death, hospitalization due to worsening HF or arrhythmic events, or SVT.

Worsening of the arrhythmic burden is defined as a 50% increase in PVC burden, or a 30% increase in NSVT at ECG 24-h ambulatory monitoring performed at 6 months after randomization, compared with baseline, or any SVT during follow-up.

Worsening imaging outcomes are defined as a reduction in LVEF of >10% at 6 months (on echocardiogram or CMRI) or, at 6-month follow-up CMRI or FDG-PET, the appearance of new areas of oedema associated with increased oedema in the inflammatory lesions identified at baseline CMRI or FDG-PET.

Improvement in imaging outcome is defined as the occurrence of the following: (1) reduction in oedema on CMRI or FDG uptake without new areas of oedema on CMRI/FDG-PET plus normal levels of high-sensitivity troponin levels, or (2) the complete resolution of oedema on CMRI or absence of FDG uptake on PET independently of the levels of troponin.

Improvement in arrhythmic outcomes is defined as (i) a 70% reduction in PVC burden on ambulatory ECG monitoring after 6 months since randomization compared with baseline without NSVT or SVT at 6 months (*Figure 2*).

A representative patient randomized at Niguarda Hospital who reached the primary efficacy endpoint is shown in *Figure 3*.

Secondary endpoints of the CMP-MYTHiC trial are presented in *Table 1*, and include the change in LVEF on CMRI, the proportion of patients with LVEF <55% and/or LV dilation at 6 months on CMRI, composite clinical outcome of all-cause mortality, heart transplantation (HTx), long-term left ventricular assist device (LVAD) or first hospitalization due to HF/VA or advanced atrioventricular block, overall mortality, presence of NSVT or increased burden of PVCs (>5%) on 24-h ECG ambulatory monitoring performed after 6 months since randomization, and changes in quality of life and health assessment questionnaires, and the need for initiating immunosuppressive therapy.

The occurrence of adverse events (AEs) and serious AEs will be monitored, with gastrointestinal symptoms, in particular diarrhoea, expected to be the most common AEs in approximately 10% of patients.[38] diarrhoea is generally dose-dependent and can reverse after discontinuation of colchicine.

Main aim of the registry

The main aim of the CMP-MYTHiC registry will be to determine whether patients carrying gene variants associated with dilated cardiomyopathies or arrhythmogenic cardiomyopathies, termed in our registry as positive MCGV (+) Infl-CMP have a worse outcome than those

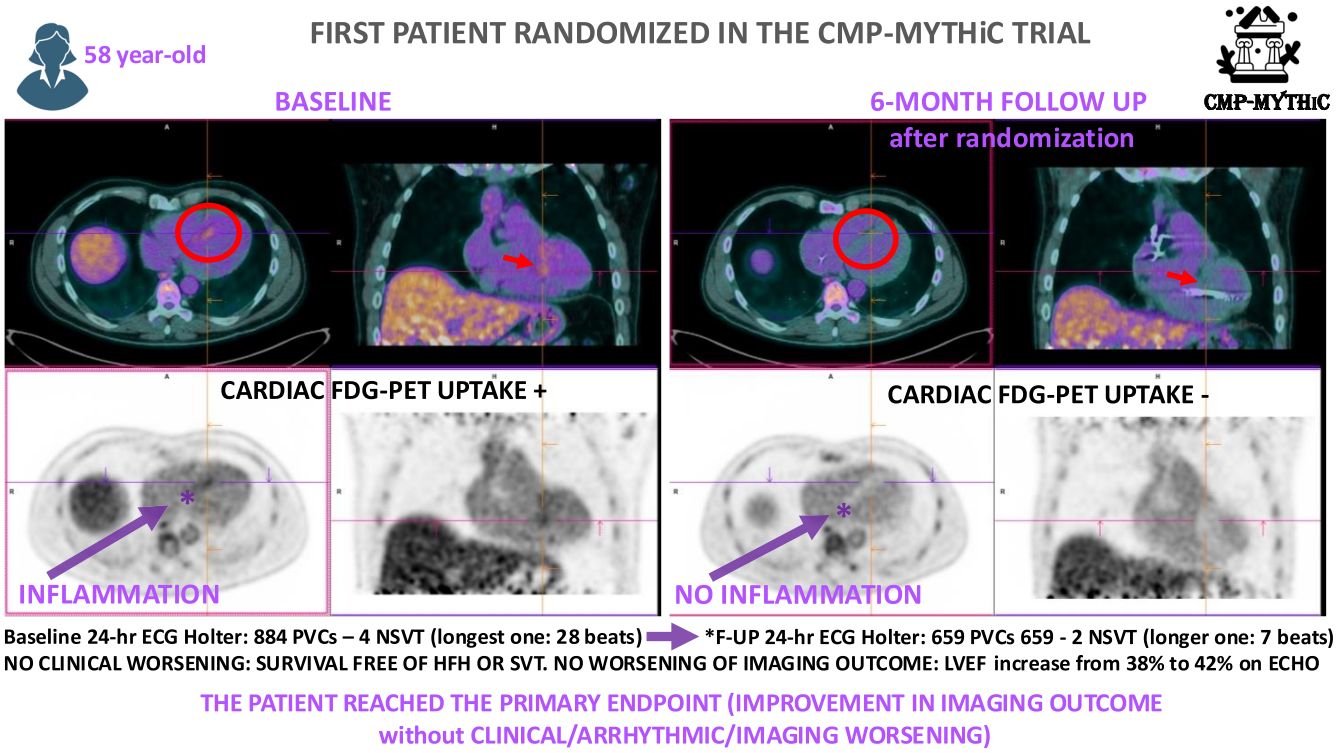

Figure 3 Representative first case randomized in the CMP-MYTHiC trial who completed the study reaching the primary outcome. A 58-year-old woman with inflammatory cardiomyopathy, as indicated by an FDG-PET scan (arrows, asterisk, and circle pointing out the FDG uptake at the level of the septum), who was eligible for the CMP-MYTHiC trial, was randomized. The arm treatment is known to the local investigators due to the single-blinded nature of the trial. The woman completed the trial reaching the primary outcome due to the improvement of the imaging outcome; in fact, there was no evidence of inflammation based on the FDG-PET scan after 6 months from randomization. CMRI, cardiac magnetic resonance imaging; ECHO, echocardiographic exam; F-UP, follow-up; FDG-PET, fluorodeoxyglucose-positron emission tomography; HFH, hospitalization due to heart failure; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; and SVT, sustained ventricular tachycardia

Table 1 Secondary endpoints of the CMP-MYTHiC trial

Secondary endpoints
1. Absolute change at 6 months from randomization of the LVEF on CMRI. **Patients not performing the CMRI due to death or HTx will be counted as −10 point in the LVEF*
2. Absolute change at 6 months from randomization of the LVEF on CMRI when available. **Patients not performing the CMRI due to death, HTx, LVAD implantation, or device implantation after randomization (i.e. PM or ICD) will be counted as −10 point in the LVEF*
3. Proportion of patients with LVEF <55% AND/OR LV dilation on 6-month CMRI or CMRI not performed due to death, HTx, LVAD implantation or device implantation after randomization (i.e. PM or ICD).
4. Composite endpoint defined as the time from randomization to the first event occurring within 6 months: (1) all-cause death or (2) HTx or (3) long-term LVAD implantation, or (5) first rehospitalization due to HF or VA, or advanced atrioventricular block
5. Mortality: time from randomization to all-cause death within 6 months
6. Time from randomization to hospitalization for HF/VA or advanced atrioventricular block within 6 months
7. Composite endpoint of presence of NSVT OR increased burden of PVCs (>5%) on 24-hour ECG ambulatory monitoring, performed at 6 months
8. Changes in quality of life and health assessment at 6 months follow-up compared with baseline using two different questionnaires: the EuroQoL five-dimension (EoQ-5D) and Kansas City Cardiomyopathy Questionnaire (KCCQ—clinical summary scale and overall summary scale).
9. Need to initiate an immunosuppressive drug (i.e. corticosteroids)

CMRI clips will be centrally reviewed.
CMRI, cardiac magnetic resonance imaging; HF, heart failure; HTx, heart transplantation; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; PM, pacemaker; PVC, premature ventricular complexes; NSVT, non-sustained ventricular tachycardia; VA, ventricular arrhythmias.

with negative MCGV (−) Infl-CMP. As the primary endpoint, we will use the same endpoint as the trial to determine whether having a positive genetic background is associated with a lower likelihood of improvement at 6 months from inclusion in the registry than having a negative genetic background. The co-primary aim will be to identify baseline variables independently associated with the 6-month endpoint. At the end of the trial, patients from the trial and the registry will be combined to confirm whether having a positive MCGV (+) Infl-CMP is associated with a worse outcome and to identify the baseline variables associated with the 6-month outcome (*Figure 4*). At present, no formal plan for merging the registry and trial cohorts has been established, and we are aware of potential biases and confounders that could affect the integrated dataset, such as slightly different inclusion/exclusion criteria. In addition, the effect of colchicine is currently unknown. The patients who enter the registry are expected to follow an even longer follow-up of 2 years, with planned visits dictated by clinical reasons and not by the study.

Statistical considerations

Sample size calculations were based on a previous prospective study that investigated the effect of prednisone in patients with Inf-CMP, showing an improvement rate of 84% in those treated with prednisone versus 33% in those not taking it (MAVERIC registry).[28] In addition, in the MAVERIC registry, 24% of patients with FDG-PET-detected inflammation had a final diagnosis of cardiac sarcoidosis, a condition likely more severe than idiopathic myocarditis, which was detected in 76% of patients. Given that we expect colchicine to have a lower anti-inflammatory effect than prednisone, but considering that patients with high-risk forms, such as histology-proven cardiac sarcoidosis, should not be included, we estimated an optimal response rate of 66% in patients receiving colchicine. In contrast, we estimated a placebo response rate of 33% in patients, similar to that observed in the MAVERIC registry. Thus, assuming an increase in the likelihood of reaching the primary endpoint at 6 months from 33% in the placebo group to 66% in the colchicine group, a planned sample size of 80 patients (40 per group) will allow achieving a power of 0.80 with an overall type I error of 0.025 using one-sided Fisher's Exact test. Primary endpoint of the trial will be analysed according to the intention-to-treat population. We planned an analysis by *per protocol* population, including only patients allocated to the colchicine arm who had taken the drug for at least 4 months. Patients assigned to the colchicine therapy arm who will receive <4 months of colchicine therapy will be excluded from this population. Likely, patients allocated to the OMT with placebo will be included if they have taken the placebo therapy for at least 4 months. Patients assigned to the treatment or placebo who will receive any immunosuppressive agents (e.g. corticosteroids) for at least 1 month during the trial will be excluded from this population. In the trial, we will compare the proportion of patients reaching the primary endpoint between colchicine and placebo using Fisher's exact test. For binary endpoints (including the primary and the main secondary endpoints), the effect of treatment will be estimated as an absolute risk difference and relative risk (with 95% confidence interval). Furthermore, to adjust for potential residual confounding not addressed by randomization, we will assess the association of treatment with the endpoints using multivariable logistic regression, adjusting for known potentially relevant variables. All time-to-event secondary endpoints will be analysed using the Kaplan–Meier method and compared between treatment groups by the log-rank test. The Cox regression model will be fitted to evaluate the association of treatment with the endpoint, adjusting for other baseline factors. Every single event included in the definition of composite endpoints will be described using competing risk methodology by estimating crude incidence functions. Continuous endpoints will be analysed using *t*-test or Mann–Whitney test depending on their distribution. Linear or quantile regression will be used to evaluate the treatment effect in a multivariable setting, adjusting for other baseline factors. The percentage of lost to follow-up will be monitored in both treatment groups. A sensitivity analysis will also be performed on the previously defined populations after excluding patients (i) with an implantable cardioverter defibrillator before randomization (ii) who underwent a ventricular ablation before randomization (iii) who were diagnosed with a systemic autoimmune disorder or a histological diagnosis of eosinophilic myocarditis, cardiac sarcoidosis, or giant cell myocarditis after randomization.

Planned subgroup analyses: The association between treatment and primary and secondary endpoints will also be analysed in the following subgroups: (i) age groups, (ii) sex, (iii) above vs. below median LVEF, (iv) with vs without previous SVT or cardiac arrest or ventricular ablation before randomization, (v) MCGV(+) vs MCGV(−). The trial was not designed to draw definite conclusions about gene-colchicine interactions, and this subgroup analysis should be seen as exploratory. The major difficulty in powering the trial for the genetic background lies in the fact that we cannot assume the proportion of patients with MCGV(+) among those eligible for the trial with Infl-CMP.

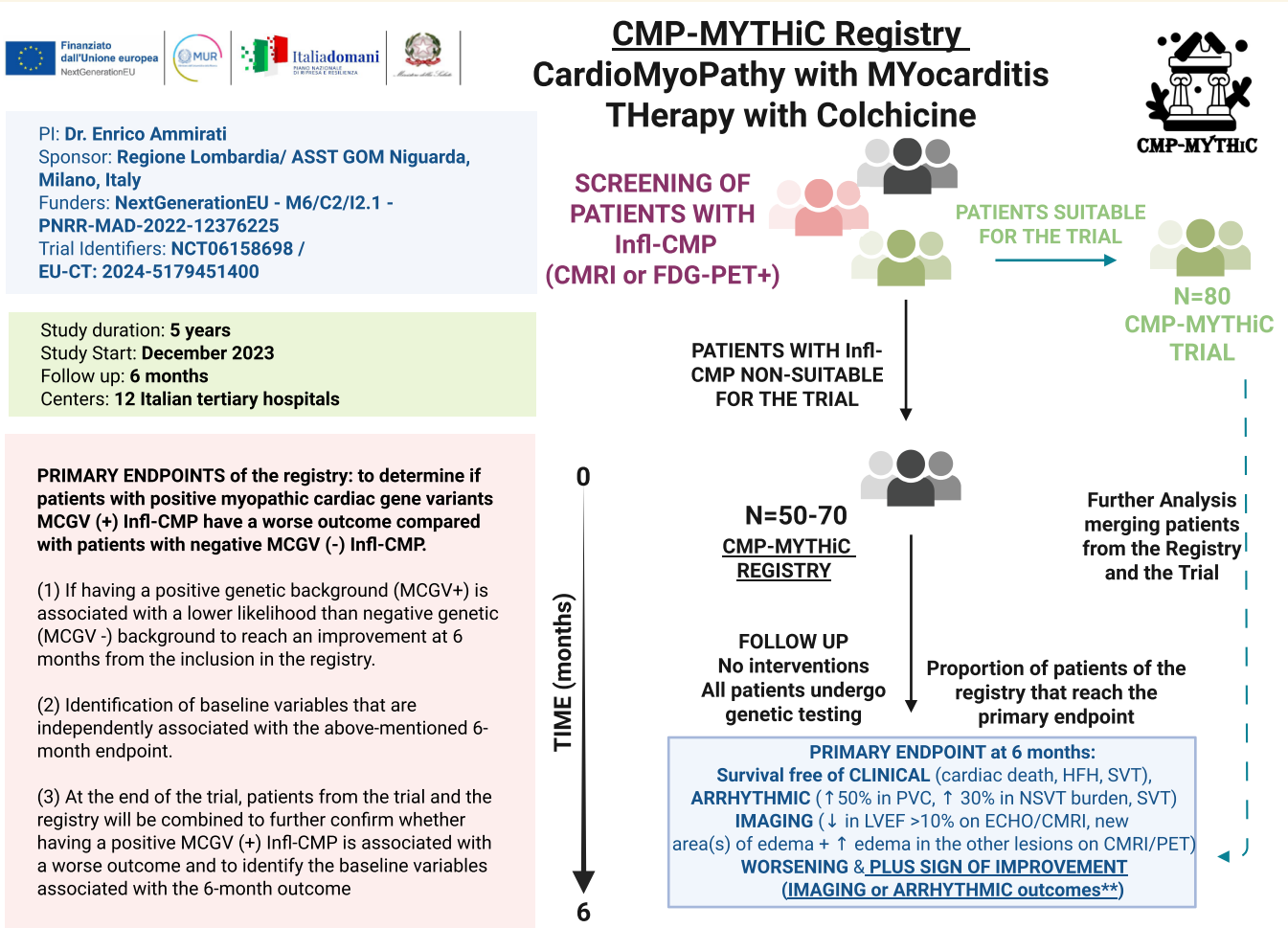

FIGURE 4 Flow chart of the CMP-MYTHiC registry. CMP, cardiomyopathy; CMRI, cardiac magnetic resonance imaging; ECHO, echocardiographic exam; FDG-PET, fluorodeoxyglucose-positron emission tomography; HFH, hospitalization due to heart failure; LVEF, left ventricular ejection fraction; MCGV, myopathic cardiac gene variants; NSVT, non-sustained ventricular tachycardia; and SVT, sustained ventricular tachycardia. In the registry, patients will be included if a non-invasive diagnosed of Infl-CMP by CMRI or FDG-PET is reached within 12 months before inclusion in the registry. Created in BioRender. Ammirati, E. (2026) https://BioRender.com/lu6i5wa

CMP-MYTHiC Registry: No sample size calculation was performed for the primary endpoint of the registry, and we will include all patients meeting the inclusion criteria, expected to be 50–70 patients during the trial.

Discussion

In patients presenting with Inf-CMP, initial therapeutic strategies often target clinical manifestations, such as HF symptoms and VA, with less emphasis on identifying the aetiological basis. Increasing recognition of inflammatory and genetic contributors could enable more targeted management strategies.[27] Few randomized controlled trials have assessed the effects of immunosuppressive therapies in acute myocarditis and chronic Infl-CMP,[11,39,40] even though there are currently no recommendations for the use of immunosuppressive agents in patients with non-invasively diagnosed Infl-CMP.[4] Colchicine, which has been observed to be potentially useful in reducing disease recurrence in patients with pericarditis and myocardial involvement in a registry,[35] may have biological plausibility for reducing myocardial inflammation in patients with Infl-CMP not secondary to cardiac sarcoidosis or systemic autoimmune disorders. Furthermore, in a randomized clinical trial, the COLICA trial, including patients with acutely decompensated HF with LVEF <40%, even if colchicine in addition to OMT did not reach the primary endpoint to reduce the time-averaged NT-proBNP levels at 8 weeks, showed a reduction in C-reactive protein and interleukin-6 levels with a lower need for intravenous furosemide during follow-up.[41] Safety profile of colchicine was further demonstrated in a large randomized controlled trial that showed its efficacy in reducing ischaemic events following acute coronary syndromes, with two AEs significantly more often observed in colchicine compared with placebo: pneumonia in 0.9% (vs 0.4% in placebo; $P = .03$) and nausea in 1.8% (versus 1.0% in placebo; $P = .02$).[33] From a molecular biology standpoint, colchicine likely exerts its effects by inhibiting pore formation induced by P2X2 and P2X7 receptors, which are activated during inflammasome signalling,[42] thus potentially targeting a specific cause observed in Infl-CMP. In a murine model of coxsackievirus 3-induced myocarditis, colchicine improves LV function by decreasing cardiac and splenic nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome activity, without exacerbating coxsackievirus load.[43] This experimental finding should reassure that colchicine should not cause viral reactivation in the myocardium. Still, because a search for viral genomes will not be performed, a potential limitation on colchicine's efficacy could be the randomization of patients with an Infl-CMP related to a persistent viral myocardial infection. Furthermore, in a rat hypertension-induced HF preserved EF model, colchicine alleviated systemic inflammation and NLRP3 inflammation activation and attenuated cardiac dysfunction and fibrosis.[44]

The evidence available to initiate immunosuppressive treatments in patients with Infl-CMP is limited. The single-centre TIMIC trial randomized 85 patients with virus-negative chronic Inf-CMP to receive either a 6-month course of prednisone plus azathioprine or standard HF medications. This combination significantly improved symptoms and echocardiographic measures in the immunosuppression group.[11] Long-term follow-up (up to 20 years) showed a lower risk of cardiovascular death and HTx in the immunosuppression group compared with a matched control cohort, with sustained improvements in LVEF. The incidence of recurrent myocarditis was similar across groups; however, patients who experienced recurrence responded positively to re-administration of the TIMIC protocol.[45] The ongoing IMPROVE-MC trial has a similar study design testing the effectiveness of prednisone plus azathioprine versus placebo in 100 patients with Infl-CMP.[46] Another more recent randomized controlled trial demonstrated a clinical benefit of hydroxychloroquine beyond prednisone in 50 patients with residual inflammation following an episode of fulminant myocarditis.[39] The limitations of this trial include the generalizability of the results and the systematic use of prednisone in all patients, including those in the placebo group. Furthermore, such a striking clinical effect of hydroxychloroquine should be confirmed in larger trials. Nevertheless, this study also contributes to increasing the knowledge on the impact of immunosuppression on patients with Infl-CMP.

Furthermore, the MAVERIC registry demonstrated that prednisone (40 mg daily for 3 months) significantly reduced the PVC burden by over 80% in 84% of treated patients, compared with 33% in untreated patients, with resolution of FDG-PET abnormalities at follow-up.[28] Nevertheless, it must be noted that the cornerstone Myocarditis Treatment Trial, the first major study to investigate immunosuppression in myocarditis, enrolling patients with histological evidence of myocarditis and cardiac symptoms in the 2 years before randomization, showed no significant improvement in LVEF or survival.[40] More recently, in the setting of acute myocarditis, the ARAMIS (Anakinra versus placebo double-blind randomized controlled trial for the treatment of Acute Myocarditis) trial that enrolled 117 symptomatic patients with acute myocarditis confirmed on CMRI, showed no benefit from daily subcutaneous anakinra (100 mg) or placebo alongside standard care during hospitalization.[47,48] Even if inhibition of the interleukin-1 pathway seems a sound therapeutic target for patients with myocarditis,[49] the ARAMIS trial likely recruited patients at low risk, with few clinically significant events. Thus, there is a need for more trials to assess the efficacy of immunosuppressive agents in patients with Infl-CMP or myocarditis. In Table 2, a list of completed or ongoing trials on immunosuppressive agents in the setting of Infl-CMP or myocarditis is presented.[9,46,50]

Rationale for the primary composite endpoint selection

The CMP-MYTHiC should be viewed as a pilot study. If the results are positive, this could inform the design of a larger study with more clearly defined clinical outcomes. The primary endpoint focuses on demonstrating a reduction in the inflammatory signal on CMRI or PET imaging. However, since the current primary endpoint emphasizes clinical outcomes, even if there is a decrease in oedema on imaging, the overall positive endpoint is not met if the patient experiences sustained VT or HF hospitalization. Similarly, a significant decrease in VA burden generally reflects a reduction in myocardial inflammation. For example, in the MAVERIC registry,[28] a decrease in FDG myocardial uptake was associated with a significant reduction in VA burden. For this reason, we also include VA burden in the composite primary outcome.

Potential trial limitations

A foreseeable limitation of this trial and registry will be the absence of a biobank and the lack of blood samples for central biomarker analysis, including troponin, natriuretic peptides, and inflammatory markers such as C-reactive protein. This is mainly due to financial constraints. In addition, we initially planned the trial, preparing only a 1 mg placebo and a 1 mg colchicine tablet. Given the tablet's small size and the availability of both 0.5 and 1 mg colchicine tablets in Italy, we are preparing an amendment in 2026 to allow both 0.5 and 1 mg tablets to be used in the trial. This is especially relevant for patients weighing <70 kg, for whom a 0.5 mg dosage is indicated in this protocol, and dividing the small size 1-mg tablet could be difficult and inaccurate. This amendment will require the production of both 0.5- and 1-mg placebo tablets. Up to now, only the 1 mg placebo and colchicine tablets have been used, but the future implementation of 0.5 mg tablets also depends on EMA approval of the amendment. Another limitation is the single-blinded nature of this trial, which can introduce potential bias compared with a double-blinded trial. However, the assessment of key imaging outcomes to determine whether a patient has experienced a reduction

Table 2 Completed and ongoing randomized controlled trials and selected studies investigating the use of immunosuppressive therapy in patients with inflammatory cardiomyopathy

Trial	Population	N.	Treatment	Outcome
Myocarditis Treatment Trial[40] (1995)	Biopsy-proven AM, LVEF <45%	111	Azathioprine 1 mg/Kg bid or ciclosporine 5 mg/kg bid (dose adjusted according to blood levels) for 24 weeks + prednisone 1.25 mg/kg (decreasing dose up to suspension in 24 weeks) ($N = 64$) vs placebo ($N = 47$)	No differences in LVEF improvement and survival at 1 year between the two groups
TIMIC[11] (2009)	biopsy-proven virus-negative lymphocytic myocarditis, LVEF <45%, chronic HF (> 6 months) unresponsive to conventional therapy	85	Prednisone 1 mg/kg for 4 weeks followed by 0.33 mg/kg for 5 months + azathioprine 2 mg/kg ($N = 43$) for 6 months vs placebo ($N = 42$)	Significant improvement in symptoms, LVEF and LV dimensions in the treatment group
ARAMIS[48] (unpublished—presented in 2023)	CMRI-proven AM within 72 hours from hospital admission	120	Anakinra 100 mg/day for 14 days ($N = 59$) vs placebo ($N = 61$)	uses of anakinra was safe but did not did not increase the number of days free of myocarditis complication
MAVERIC registry[28] (2019)	Positive FDG-PET and PVC > 5000/24 hours	55	Oral prednisone 40 mg for 3 months ($N = 32$), oral prednisone 40 mg + catheter ablation ($N = 14$), OMT ($N = 9$)	reduction of PVC burden and resolution of FDG-PET uptake in patients treated with prednisone
MYTHS trial[9]	suspected AM complicated by acute HF/cardiogenic shock, LVEF <41%, LVEDD <56 mm	288	Methylprednisolone 1 g for 3 days ($N = 144$) vs placebo ($N = 144$)	Ongoing
IMPROVE-MC trial[46]	Patients with biopsy-proven virus-negative AM or inflammatory cardiomyopathy and reduced LVEF (≤ 45%)	100	Predinisone 1 mg/kg for 2 weeks followed by tapered dose + azathioprine 2 mg/kg daily for 12 months ($N = 50$) vs placebo ($N = 50$)	Ongoing
ARCHER trial[50]	Biopsy or CMR-proven AM	100	Pharmaceutically produced cannabidiol formulation 2,5–10 mg bid vs placebo	Ongoing
HYPIC trial[39] (2025)	Chronic inflammatory cardiomyopathy after fulminant AM	50	HCQ 200 mg + prednisolone 20 mg ($N = 25$) vs prednisolone 20 mg ($N = 25$) for 1 year	Reduction of the composite outcome (time to cardiovascular death or heart transplant, hospitalization for HF, recurrence of AM, PM or ICD implantation)
Immunosuppressive Therapy and Risk Stratification of Patients With Myocarditis Presenting With VA registry[29] (2020)	Biopsy and CMRI-proven virus-negative AM and VA	116	1 mg/kg prednisone progressively tapered and 2 mg/kg azathioprine (or other immunosuppressors in case of intolerance) for 12 months ($N = 58$) vs placebo ($N = 58$)	Improvement in NSVT and PVC burden. No difference in major VA.

AM, acute myocarditis, CMRI, cardiac magnetic resonance imaging, LVEF, left ventricular ejection fraction, FDG-PET, fluorodeoxyglucose-positron emission tomography scan; HF, heart failure, LV, left ventricle, LVEDD, left ventricular end diastolic diameter; ICD, implantable cardioverter defibrillator; PM, pacemaker; PVC, premature ventricular complexes, HCQ, hydroxychloroquine, VA, ventricular arrythmias, NSVT, non-sustained ventricular tachycardia.

in myocardial inflammation on CMRI or FDG-PET will be conducted centrally by blinded physicians, limiting the potential bias on the primary endpoint. While CMRI and FDG-PET results will be centrally adjudicated in a blinded manner, the ECG 24-h ambulatory monitor readings will be interpreted locally and are expected to be performed mainly by independent physicians unaware of the assigned treatments. In addition, we expect that most patients in the CMP-MYTHiC trial will not have histological confirmation of Infl-CMP, an inherent limitation of the study. Likewise, analyses to differentiate between myocardial inflammation with or without viral genomes in the myocardium will not be possible; thus, we will not assess the interaction between viral presence in the heart and colchicine. Another potential limitation related to the absence of histology in a proportion of patients who will enter the study is the uncertainty in ruling out specific forms, such as

sarcoidosis and giant cell myocarditis. FDG-PET usually allows for the identification of patients with high suspicion for sarcoidosis due to FDG uptake in other organs, such as hilar nodes and lungs. In those cases, EMB can be considered before including patients in the study, but this decision is for the local investigators. Giant cell myocarditis generally presents with a severe clinical scenario with refractory HF,[6,51] which should generally trigger the execution of EMB. In this trial, we aim to identify a *grey zone* of patients in whom an EMB is often not performed immediately, or if performed, is not particularly useful in guiding treatment. Importantly, after 6 months, when patients undergo follow-up imaging, the investigators may decide to perform an EMB if inflammation persists or anticipate an EMB in case of significant clinical deterioration.

Regarding the inclusion criteria, we arbitrarily set two thresholds to define reduced LVEF for trial entry based on echocardiogram examination and CMRI. It is expected that most patients will enter the trial based on the criteria of myocardial inflammation and LVEF <60% on CMRI. We considered normal values for LVEF between 52 and 72% for both sexes,[52] and for CMRI between 57% and 77%.[53] Thus, we will likely also include patients with LVEF in the low-normal range based on CMRI criteria, while we will be more conservative in including patients with LVEF reduction based on echocardiographic criteria. Nevertheless, differences in the inclusion criterion for LVEF based on echocardiography or CMRI are not expected to affect the trial results. Also, the trial's inclusion PVC threshold is arbitrary. Compared with the MAVERIC registry,[28] a new analysis from the DSP-ERADOS (Desmoplakin Specific Effort for a Rare Disease Outcome Study) showed that patients with DSP-associated cardiomyopathy who experience a ventricular arrhythmic event during follow-up have an interquartile range of PVCs of 798–4519, with a median of 2000.[54] In addition, it is expected that a certain proportion of patients with Infl-CMP can have a P or LP *DSP* genetic variant.[18,55] Based on this finding, we have decided to request, in the next trial amendment, the inclusion of all patients with ≥500 PVC/24-h, independent of troponin levels, both in the trial and the registry. We will exclude patients who could have undergone an EMB with evidence of focal myocarditis and negative CMRI or FDG-PET solely because the quantification of changes in inflammation at 6-month follow-up by imaging can be unreliable for assessing the primary endpoint. Excluding these patients with focal myocarditis on histology and negative imaging could reduce the generalizability of our future results to only patients where CMRI or FDG-PET demonstrates inflammation. Along the same lines, excluding all women of childbearing potential due to insufficient data on the embryo-fetal risks associated with colchicine can limit the generalizability of the trial's results.

Conclusions

An improved understanding of genotype-phenotype relationships, along with better molecular mechanistic insights in Infl-CMP, will enable more targeted therapy. The CMP-MHYTiC trial will investigate the potential role of colchicine in reducing myocardial inflammation and improving clinical outcomes in patients with inflammatory CMP, and will systematically examine genotype in phenotypically well-characterized patients. Our results could provide initial observations to inform the design of larger trials assessing the effect of colchicine, a low-cost immunomodulating drug, in patients with Infl-CMP, both with and without associated genetic variants.

Supplementary data

Supplementary data are available at *ESC Heart Failure* online.

Acknowledgements

Regione Lombardia supported the study as sponsor with the ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy. Acarpia, which freely provided colchicine and the placebo. Packaging and distribution of colchicine and placebo is performed by Euromed Pharma Services s.r.l. All CMRI and FDG-PET are analysed centrally by the Imaging Core Laboratory at Niguarda Hospital, Milano, Italy. Istituto di Ricerche Farmacologiche Mario Negri IRCSS (Milano, Italy) is responsible for the overall data management and management of local Contract Research Organizations. Data Safety Monitoring Committee: Chief: Paolo Camici (San Raffaele Hospital, Milano), Aldo Maggioni (Centro Studi ANMCO, Firenze), Antonio Abbate (University of Virginia, VA, USA), Giulia Barbati (Biostatistics Unit, Department of Medical Sciences, University of Trieste). Pharmacovigilance is performed by the University of Milano.

Declarations

Disclosure of Interest

The principal investigator has received another grant from the Italian Ministry of Health (GR-2019-12368506) and is a consultant for Lexeo, and previously served as a consultant for Hotgen Health Inc.

Funding

Funded by the European Union, NextGenerationEU—Mission 6/Component 2/Investment 2.1/PNRR—CUP H43C21000150006. E.A. is the principal investigator, while M.L.N. and F.S.L. are collaborators on the grant PNRR-MAD-2022-12376225.

Ethical Approval

Approval was obtained at the Italian (initial approval by the Agenzia Italiana del Farmaco with the EudraCT identifier 2022-003912-99 on 26 April 2023) and European levels [approved transition by the European Medicines Agency (EMA) with the EU-CT number: 2024-5179451400 on 28 October 2024], as well as from institutional review boards at each participating centre (approval from Comitato Etico Milano Area 3 on date 11 May 2023 for the coordinating centre ASST Grande Ospedale Metropolitano Niguarda in Milano, Italy).

Pre-registered Clinical Trial Number

NCT06158698.

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