

Colchicine in acute heart failure: Rationale and design of a randomized double-blind placebo-controlled trial (COLICA)

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Aims

Heart failure (HF) elicits a pro-inflammatory state, which is associated with impaired clinical outcomes, but no anti-inflammatory therapies have demonstrated a clinical benefit yet. Inflammatory pathways related with the interleukin-1 axis are overactivated during episodes of acute HF. Colchicine, an anti-inflammatory drug with proven benefits in acute pericarditis and ischaemic heart disease, may target this inflammatory response. This study aims to assess the efficacy of colchicine in acute HF patients.

Methods

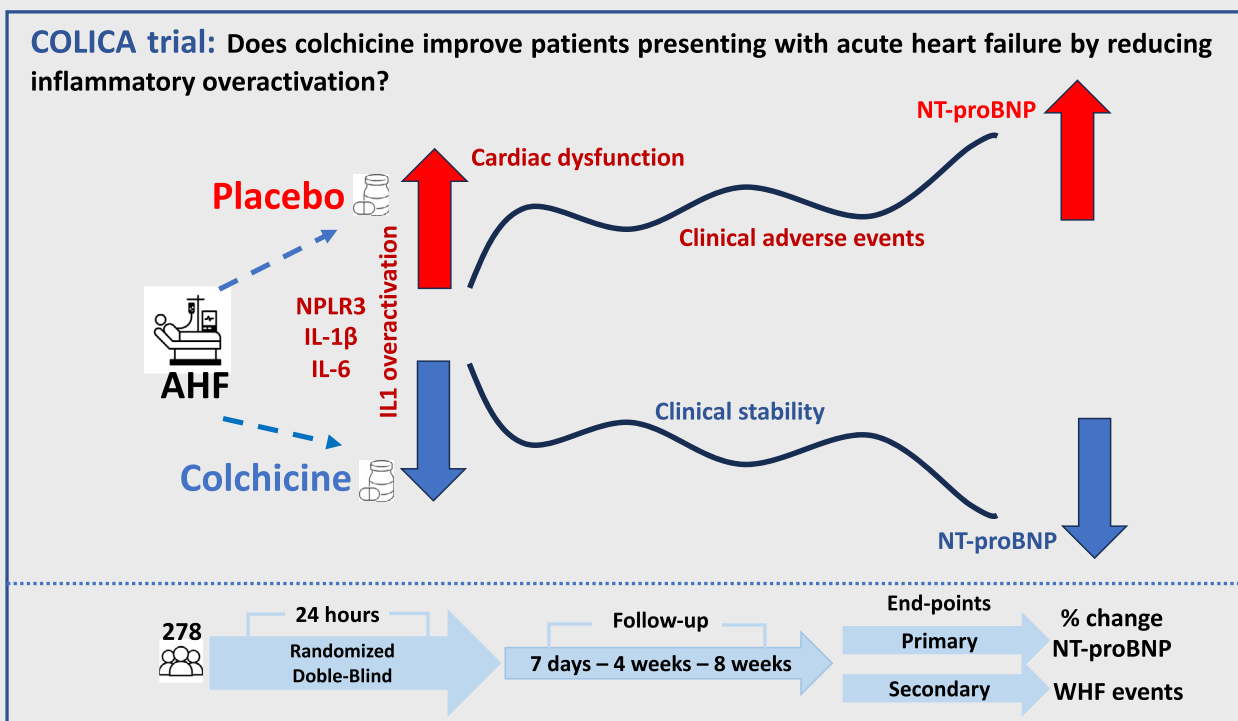
COLICA is a multicentre, randomized, double-blind, placebo-controlled trial enrolling 278 patients across 12 sites. Patients presenting with acute HF, clinical evidence of congestion requiring ≥ 40 mg of intravenous furosemide and N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 900 pg/ml, are eligible for participation. Patients are enrolled irrespective of left ventricular ejection fraction, HF type (new-onset or not) and setting (hospital or outpatient clinic). Patients are randomized 1:1 within the first 24 h of presentation to either placebo or colchicine, with an initial loading dose of 2 mg followed by 0.5 mg every 12 h for 8 weeks (reduced dose if < 70 kg, > 75 years old, or glomerular filtration rate < 50 ml/min/1.73 m²). The primary efficacy endpoint is the time-averaged proportional change in NT-proBNP concentrations from baseline to week 8. Key secondary and exploratory outcomes include symptoms, diuretic use, worsening HF episodes, related biomarkers of cardiac stress and inflammation, total and cardiovascular readmissions, mortality and safety events.

Conclusion

COLICA will be the first randomized trial testing the efficacy and safety of colchicine for acute HF.

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Graphical Abstract



Schematic representation of the rationale and design of the COLICA study: acute heart failure (AHF) is associated with an overactivation of the interleukin (IL)-1 axis and elevated pro-inflammatory cytokines, which causes cardiac dysfunction and facilitates clinical adverse events. The anti-inflammatory effect of colchicine, initiated within the first 24 h after AHF presentation, will facilitate clinical stability through such vulnerable period, including lower levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and lower rates of worsening heart failure (WHF) at 8 weeks, as compared with placebo.

Keywords

Heart failure • Colchicine • Inflammation • Randomized controlled trial

Introduction

A close relationship between cardiovascular disease and inflammation has been observed in experimental and clinical research for many years. In patients with heart failure (HF), inflammation has been linked to disease development and progression and correlates with worse outcomes.¹ Unfortunately, this knowledge has not led to anti-inflammatory therapies with well-recognized benefits, such is the case of anti-cytokine therapies or steroids.^{2–5} The majority of studies have focused on anti-inflammatory drugs in chronic HF patients who display low-grade inflammation.² On the other hand, numerous studies have demonstrated a greater activation of inflammatory pathways in patients with acute HF (AHF), which is associated with adverse clinical events during follow-up and, in particular, during the early period after discharge (so-called ‘vulnerable period’).⁶

Although several inflammatory biomarkers have been linked to HF, the interleukin-1 (IL-1) axis is markedly overactivated

in AHF syndromes. Furthermore, elevated concentrations of related cytokines (IL-1 β and IL-6) and acute-phase proteins (such as C-reactive protein [CRP]) have been repeatedly associated with adverse clinical events.⁷ Blockade of the IL-1 axis by using a receptor monoclonal antibody against the IL-1 receptor has yielded conflicting results in terms of functional capacity in patients with chronic HF.^{8–10} Recently, direct inhibition of IL-1 β with canakinumab has been found to prevent HF-related events in patients with prior myocardial infarction.¹¹ Colchicine is an old and inexpensive anti-inflammatory drug that inhibits the activation of inflammasome and the expression of various cytokines along the IL-1 axis, such as IL-1 β , IL-6, and IL-18.¹² Colchicine is the only anti-inflammatory drug approved in cardiovascular diseases, for preventing recurrences of pericarditis and, recently, for reducing cardiovascular events among adults who have established atherosclerotic cardiovascular disease or are at risk of developing it.^{13–15} However, only one randomized controlled trial (RCT)

has investigated the efficacy and safety of low-dose colchicine in patients with stable chronic HF; at 6 months, colchicine was safe and reduced inflammatory markers but did not improve clinical endpoints.¹⁶

Our hypothesis posits that colchicine confers benefits to individuals suffering from AHF by attenuating the exaggerated activation of inflammatory pathways. Consequently, we designed a trial to investigate whether the early initiation of colchicine facilitates clinical stability by reducing levels of natriuretic peptides and preventing new worsening HF episodes.

Methods

Study design

COLICA is a phase III, multicentre, randomized, double-blind and placebo-controlled trial designed to assess the safety and efficacy of colchicine compared to placebo in patients diagnosed with AHF (Figure 1). Planned enrolment of 278 patients will occur at 11 participating centres in Spain and one in Italy.

Study population

Patients aged 18 years or older presenting with a diagnosis of AHF will be screened within the first 24 h after presentation. AHF is diagnosed based on symptoms and signs of clinical congestion, need for intravenous diuretics and elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) >900 pg/ml. Patients are eligible irrespective of a previous history of HF (i.e. new-onset or worsening chronic HF), left ventricular ejection fraction (LVEF) – preserved or reduced – and setting care (hospital admission or urgent ambulatory visit). Patients meeting all the inclusion criteria and none of the exclusion criteria (outlined in Table 1) may be eligible for study participation.

Randomization and study drug

Randomization is performed using a web-based system, and stratified by age (<60 vs. 60–75 vs. >75 years), gender (male vs. female), baseline NT-proBNP levels (900–2500 vs. 2500–5000 vs. >5000 pg/ml),

new-onset HF (yes vs. no), LVEF (<40% vs. ≥40%), atrial fibrillation (yes vs. no) and care setting (hospital vs. outpatient). This stratification intends to control the distribution between groups of those variables that potentially influence NT-proBNP response, without affecting the potency of randomization. Both patients and investigators are blinded to the therapy group (placebo or active drug). The study drug is initiated within 24 h after presentation. Patients receive a loading dose of 2 mg (1.5 mg initially, followed by an additional 0.5 mg after 1 h) and a maintenance dose of 0.5 mg twice daily for 8 weeks. For patients with reduced weight (<70 kg), elderly (>75 years old), or with a decreased renal function (glomerular filtration rate <50 ml/min/1.73 m²), a reduced dosing regimen is employed: starting with a reduced initial dose of 1.5 mg (1 mg initially, followed by 0.5 mg after 1 h), and a daily maintenance dose of 0.5 mg per day during 8 weeks.

Study endpoints

The primary endpoint is the change in NT-proBNP concentration from baseline through week 8, as a surrogate biomarker of congestion, disease status and stability. In addition, several events reflecting worsening HF are included as secondary efficacy endpoints to assess the effect in terms of clinical stability. NT-proBNP concentrations will be measured centrally at the end of the study. Among other secondary and exploratory endpoints: symptoms are assessed by the New York Heart Association (NYHA) class and using the visual analogue scale (VAS) and the 7-point Likert scale; other related biomarkers reflecting cardiac stress and inflammation will be measured (high-sensitivity troponin T, CRP, IL-1β, IL-6, soluble suppressor of tumorigenicity-2 [ST2], and carbohydrate antigen 125). Among safety adverse events, gastrointestinal and haematologic disorders, infection, renal and hepatic function are considered of special interest. All study endpoints are listed in Table 2.

Follow-up and study procedures

Follow-up visits are conducted at 7 days, 4 weeks and 8 weeks after randomization. The final visit takes place in 8 weeks. The last dose of the blinded study drug is administered on the morning of the week 8

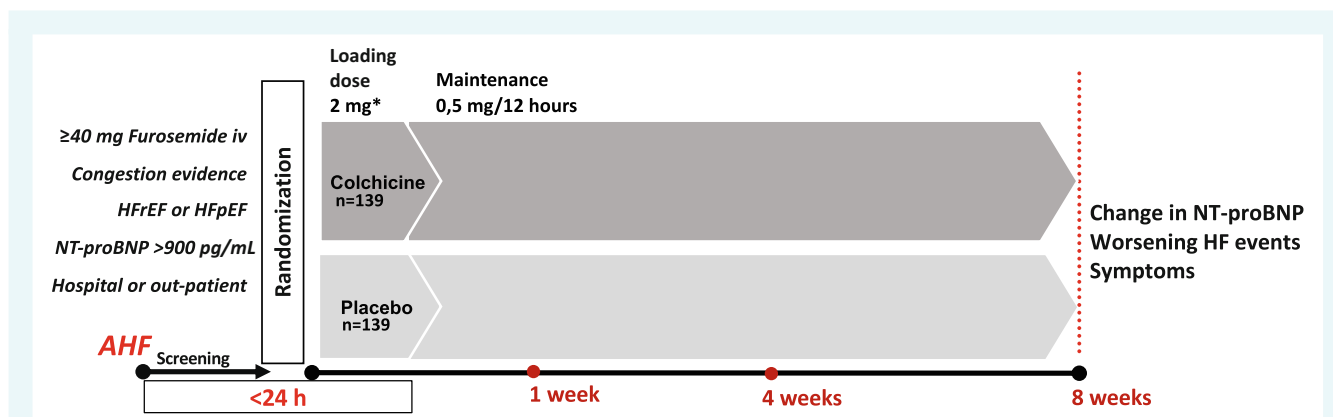


Figure 1 Schematic flow-diagram of the study. AHF, acute heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; iv, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide. *If <70 kg or >75 years or glomerular filtration rate <50 ml/min/1.73 m²: loading dose 1.5 mg (1 mg followed by 0.5 mg after 1 h), and daily maintenance dose of 0.5 mg.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> • Unplanned visit for symptoms or signs of congestion due to HF and requiring at least 40 mg of intravenous furosemide • Clinical or radiological evidence of congestion • NT-proBNP concentration >900 pg/ml • Patients >18 years of age and provided written informed consent
Exclusion criteria	<ul style="list-style-type: none"> • Severe valvular heart disease with an indication for surgery • Non-cardiac disease with life expectancy of <1 year • Inflammatory bowel disease, chronic diarrhoea or malabsorptive disease • Any severe gastrointestinal disease • Peptic ulcer • Rheumatic inflammatory disease • Neuromuscular disease • Haematologic disease such as blood dyscrasias • Severe renal impairment (eGFR <30 ml/min/1.73 m²) • History of cirrhosis, chronic active hepatitis, or severe hepatic disease (defined by GOT or GPT levels >×3 upper limit of normal) • Patients currently taking colchicine for other indication • History of allergic reaction or hypersensitivity to colchicine • Chronic treatment with immunosuppressants, steroids or IL-1 antagonists in the 6 previous months to inclusion • Pregnant or nursing (lactating) women • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant unless they are using two birth control methods.

eGFR, estimated glomerular filtration rate; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HF, heart failure; IL-1, interleukin-1; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Study endpoints and measures

Primary endpoint	<ul style="list-style-type: none"> • Time-averaged proportional change in NT-proBNP from baseline
Secondary endpoints	<ul style="list-style-type: none"> • Total dosage and length of use of IV loop diuretics during the index episode • Symptoms assessed by the visual analogue scale, 7-point Likert scale and NYHA functional classification • 'Worsening HF episodes', defined as the need for IV diuretics or for increasing oral diuretic doses, in either a planned or unplanned visit, with or without hospitalization • 'Acute worsening HF episodes' defined as the need for IV diuretics in an unplanned visit, with or without hospitalization • Time to first recurrent HF hospitalization • Rate of HF rehospitalizations, total HF rehospitalizations and total days of HF hospitalization • Time to cardiovascular death or HF rehospitalization • Time to death or hospitalization for any cause • Rates of total mortality, cardiovascular mortality, HF-related mortality and sudden cardiac death • Change in concentrations of related biomarkers from baseline to 8 weeks: hsTnT, C-reactive protein, IL-1β, IL-6, sST2 and CA125 • Severity of worsening HF episodes defined by need for ICU admission or inotropes • Total resource consumption: total days of hospitalization, number of urgent care visits or unplanned visits for worsening HF episodes

CA125, carbohydrate antigen 125; HF, heart failure; hsTnT, high-sensitivity troponin T; ICU, intensive care unit; IL, interleukin; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sST2, soluble suppressor of tumorigenicity-2.

visit. The study procedures are shown in Table 3. Blood samples will be stored for measuring NT-proBNP concentrations and for pre-specified post-hoc analysis.

Statistical plan

The sample size was calculated considering a statistical significance threshold of 0.05, a statistical power of 80%, and an expected loss of 25%. A sample size of 278 patients (139 per group) was planned

to detect a 25% greater time-averaged proportional reduction in NT-proBNP levels, from baseline to week 8, in the colchicine group compared to the placebo group, considering a variability of 0.75 in both groups. NT-proBNP levels will be logarithmically transformed due to the expected non-normal distribution of values. The changes in the transformed variable are equivalent to the geometric mean, and the expected reduction of 25% is consistent with the rate observed in the PIONEER-HF study, which had a similar design.¹⁷ All endpoints will be evaluated based on the intention-to-treat principle. Changes from

Table 3 Study procedures

Visit	Screening randomization	Visit 1	Visit 2	Final visit
Week	0	1	4	8
Days	0	7 ± 1	28 ± 2	56 ± 2
Informed consent	X			
Demographics	X			
Medical history	X			
Local blood test ^a	X			X
Pregnancy test	X			
Electrocardiogram	X			X
Vital signs ^b	X	X	X	X
NYHA class, VAS and 7-point Likert scales	X	X	X	X
Patient-reported outcomes	X	X	X	X
Study events		X	X	X
Adverse events		X	X	X
Medication reconciliation	X	X	X	X
Biobank	X	X	X	X

NYHA, New York Heart Association; VAS, visual analogue scale.

^aLocal blood test: sodium, potassium, creatinine, estimated glomerular filtration rate, blood count, N-terminal pro-B-type natriuretic peptide, troponin T, liver function test, uric acid, lipid panel, C-reactive protein.

^bWeight, height, blood pressure, and heart rate.

baseline in NT-proBNP levels will be compared between groups using a mixed-design model (ANOVA with a within-subjects variable [time: baseline and final] and a between-subjects variable [group: placebo and colchicine]), and considering baseline NT-proBNP levels and occurrence of acute worsening HF events as covariates. The trajectories of NT-proBNP levels over time will be described and drawn, and changes at 1 week and at 4 weeks from baseline will be also compared between groups. Tukey test or multiple comparisons with Bonferroni–Holm correction will be performed for post-hoc analysis. Comparisons will be made for those significant effects, assuming homoscedasticity or not. Exploratory analysis by group (placebo vs. colchicine) will be performed for secondary endpoints, such as scatter plots, bar charts, histograms and boxplots. Variables related to medication requirement or number of events will be analysed both dichotomously by time and group (McNemar test) and continuously (mixed model ANOVA or Brunner–Langer non-parametric model). Ordinal categorical variables such as the NYHA class or the symptom scales will be studied using the non-parametric Brunner–Langer model, and continuous variables, using mixed ANOVA models. In cases with different time trends observed between groups (placebo vs. colchicine), hierarchical linear models (aka linear mixed-effects models or multilevel models) will be fitted to adjust for relevant covariates. In order to analyse adverse events and time-to-event variables, survival analysis will be performed, including Kaplan–Meier plots and proportional hazards Cox models adjusting for covariates. In the presence of competing risks (such as new hospitalization or death), Cox regression models will be performed on the combined event and competing risk models with cumulative incidence curves and Fine–Gray regressions will be fitted. All data analysis will be performed at the end of the study in a centralized manner, without intermediate analyses before the end of data collection. The significance level used will be 0.05 and the null hypothesis (H0) will be the non-existence of differences (two-tailed tests) in all cases. R software will be used for all analyses.

Ethical and administrative considerations

The COLICA trial complies with the Declaration of Helsinki and Good Clinical Practice guidelines. The National Agency of Medications and Health Care Products (AEMPS) (MUH/CLIN/EC) and the institutional review board at each participating centre independently approved the protocol (IMIB-CO-2020-01) (21 August 2020). Written informed consent was obtained from all study participants before enrolment. The COLICA trial is registered at EudraCT (2020–000941-15), CTIS (EU CT 2023–504 165-23) and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04705987) (NCT04705987).

Discussion

Heart failure is a complex disease in which decongestion and modulation of neurohormonal compensatory mechanisms have been the main therapeutic strategy. However, inflammation is present in HF with increased circulating levels of pro-inflammatory cytokines and decreased anti-inflammatory cytokines.¹⁸ This pro-inflammatory state causes ventricular dysfunction and myocardial adverse remodelling, as well as vascular and peripheral organ dysfunction, which accelerates disease progression and promotes greater instability.^{1,2} Indeed, inflammatory parameters (CRP, tumour necrosis factor [TNF]- α , IL-6, IL-1 β and ST2, among others) are elevated in patients with chronic HF, and they are highly up-regulated during the acute phases^{2,6}. These augmented levels are associated with worse prognosis and higher risk of death and hospitalization.^{1,2,6} Furthermore, the prognostic value of all these interleukins is independent of LVEF. Therefore, there is a large knowledge linking inflammation with accelerated disease progression. For this reason, studies aimed at reducing this inflammatory state in patients with HF have been conducted, but they failed to demonstrate a significant clinical benefit. These may be

explained by using certain cytokines as therapeutic targets, which do not actively participate in the disease (e.g. TNF- α),^{3,4} or by not selecting the proper population, for example, stable chronic HF patients, where the role of inflammation may be less relevant compared with other pathophysiological processes.^{6,19}

Role of the interleukin-1 axis

The IL-1 axis includes a family of ILs with different receptors. IL-1 β is an upstream mediator, and its production follows immediately inflammasome activation. IL-1 β has proven a causal role in the progression of atherosclerosis and ventricular dysfunction in experimental models.²⁰ IL-1 β is also markedly elevated in AHF patients, identifying those with a worse prognosis.⁷ There is much experimental evidence indicating that IL-1 β administration impairs both myocardial contractility and relaxation, and induces reversible non-ischaemic cardiomyopathy.²¹ Interestingly, injecting mice with plasma obtained from patients with AHF produces impairments in systolic function, which can be prevented by pre-treatment with an anti-IL-1 antibody.²² IL-6 acts downstream of the IL-1 axis; it is the primary stimulus for the liver production of CRP and mediates the transition from acute to chronic inflammation. IL-6 elevation is associated with impaired myocardial function and remodelling and has deleterious effects on other organs, including impaired natriuresis and renal function, and resistance to diuretics.⁶ Infusion of IL-6 causes diastolic dysfunction that can be reversed with the IL-6 receptor antagonist tocilizumab, as well as cardiomyocyte hypertrophy and fibrosis.²³ CRP does not have an active role, but as an acute-phase reactant protein identifies overactivation of the IL-1/IL-6 axis and has been consistently associated with a worse prognosis. Therefore, several trials have used this marker of inflammation to identify patients with an inflammatory status, even considering the lack of specificity of this acute-phase reactant. Overall, the IL-1 axis is a relevant inflammatory pathway in HF, with a role in disease progression based on experimental studies, and it is over-activated in patients, identifying a worse prognosis.

Role of interleukin-1-based anti-inflammatory therapies

Blockade of the IL-1 axis may be achieved by specific therapies, either blocking directly IL-1 β (canakinumab) or IL-6 (Ziltivekimab), the IL-1 receptor (anakinra) or the IL-6 receptor (tocilizumab), or by non-specific therapies (colchicine). First, anakinra was shown to improve cardiac function in a small study of patients with rheumatoid arthritis.²² In two small RCTs, patients with HF and preserved LVEF (Diastolic Heart Failure Anakinra Response Trial [D-HART Pilot], $n=12$; and D-HART2, $n=31$) anakinra increased peak oxygen consumption (VO_2) at 2 weeks, but no improvement was obtained after 12 weeks compared with placebo.^{9,24} RED-HART (Recently Decompensated Heart Failure Anakinra Response Trial) enrolled HF patients with LVEF $<50\%$ and CRP >2 mg/dl within 14 days of hospital discharge. Patients receiving 12 weeks of anakinra had significantly lower CRP levels and improved peak VO_2 and exhibited a trend toward lower rates of death or HF hospitalization

after 24 weeks.⁸ In another small RCT ($n=30$) that recruited patients within 24 of admission with AHF (LVEF $<40\%$), anakinra was associated with a greater reduction of CRP at 14 days, without differences in the length of hospital stay.¹⁰ No clinical trial has specifically evaluated the effects of IL-6 blockade in HF. In patients with rheumatoid arthritis, tocilizumab was associated with improvements in cardiac function and remodelling parameters measured by cardiac magnetic resonance imaging.²⁵ The most encouraging results have been achieved with canakinumab, a monoclonal antibody directed to block IL-1 β . The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial found that in participants who responded to canakinumab (as evidenced by a reduction in CRP to <2 mg/L), IL-1 β blockade was associated with a significant 38% reduction in HF hospitalizations and a 32% reduction in the composite of HF hospitalizations and all-cause death, compared with placebo.¹¹ This benefit was observed in both patients with or without a history of HF. However, adoption of this strategy was limited by an unfavourable cost-benefit balance and a higher rate of fatal infections.^{5,12}

Rationale for the use of colchicine

Colchicine is an old, inexpensive and safe drug with good anti-inflammatory activity.¹² Among the multiple anti-inflammatory mechanisms of action, the inhibition of the inflammasome, responsible for the conversion of pro-IL-1 to IL-1 β , is a main determinant of the beneficial effects of colchicine in cardiovascular diseases.^{21,26} Other mechanisms include the inhibition of neutrophil migration by blocking tubulin polymerization and microtubule formation, and the inhibition of IL-1 production in activated neutrophils, and the reduction of other inflammatory chemokines such as IL-6 and IL-18.²⁷ In cardiovascular disease, colchicine is indicated for the treatment of acute pericarditis to prevent recurrences.^{13,28} It has also shown efficacy in other cardiovascular conditions mediated by inflammation, such as post-pericardiotomy syndrome and atrial fibrillation after cardiac surgery or pulmonary vein isolation.¹³ Recently, low-dose colchicine has proved effective in chronic coronary artery disease, mainly because of a reduced risk of stroke and coronary revascularization, with a similar incidence of adverse events as placebo.^{14,29} Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischaemic cardiovascular events than placebo.¹⁵ This has recently led to the U.S. Food and Drug Administration approval of colchicine as the first anti-inflammatory drug for patients who have established atherosclerotic cardiovascular disease or are at risk of developing it, which raises interest in studying colchicine for other cardiovascular conditions where inflammation is relevant such as HF. Indeed, colchicine reduces myocardial stiffness and cardiac hypertrophy in pre-clinical models of HF.^{12,30} There is only one previous RCT studying colchicine in chronic HF, where treatment with colchicine for 6 months, although effective in reducing inflammatory biomarkers, was not effective in reducing clinical endpoints or improving functional status for patients with stable HF and reduced LVEF.⁶ In a retrospective study evaluating the role of colchicine in treating acute gout flares in patients with AHF, colchicine use was associated with a lower

rate of all-cause and cardiovascular mortality during the index hospitalization, without significant differences in 30-day readmission rates.³¹ Therefore, considering that colchicine has shown a benefit in several cardiovascular disorders where the inflammatory IL-1 axis is over-activated, it is plausible to expect a benefit in patients with HF, and a dedicated RCT is needed to define its role in this syndrome.

Rationale for the selected population, short-duration treatment and endpoints

There are several reasons to hypothesize that colchicine may prove effective in patients with AHF. First, related cytokines are significantly more elevated in the acute setting, at admission, and identify a higher risk of adverse clinical events at follow-up.⁶ Second, AHF patients are prone to suffer new worsening HF episodes and have a higher risk of death, which persists during the early post-discharge period. Based on these premises, starting an anti-inflammatory therapy as early as possible (within 24 h of diagnosis) may be effective by blunting the over-activated inflammatory status. A short-duration treatment (8 weeks) with an anti-inflammatory drug can be beneficial in order to deal with the vulnerable period after the AHF episode ($\approx 1-2$ months) and avoid the potential adverse side effects associated with a longer administration.

We decided to enrol patients with the whole spectrum of LVEF, considering that inflammation is present and predictive of complications irrespective of LVEF. Contrary to most previous RCTs, we did not include among selection criteria a specific threshold of CRP levels. We recognized that the identification of an inflammatory status may be relevant in chronic patients with low grades of inflammation. However, in patients suffering AHF, the presence of inflammation may be taken for granted, and CRP levels are not a fair indicator in the acute phase (0–24 h) given that serum levels tend to increase significantly 6–8 h after the stimulus but peak occurs around 48 h.³² Therefore, we opted for a pragmatic approach where the clinical diagnosis of AHF takes priority by intending to start the anti-inflammatory therapy within the first 24 h.

The primary endpoint is the decrease in NT-proBNP concentrations as a well-established marker that may be used as a surrogate of severity and clinical outcomes. We used a similar design to the PIONEER-HF trial, where the use of sacubitril/valsartan showed a reduction in NT-proBNP levels at 8 weeks, as well as a reduction in secondary clinical endpoints reflecting worsening HF. We also included, as secondary endpoints, HF-related clinical events to assess disease stability with different definitions, as well as non-cardiovascular events (including drug-related adverse events) and the response of other relevant biomarkers of cardiac stress and inflammation.

Limitations

A surrogate primary efficacy endpoint, NT-proBNP, was chosen because of financial constraints precluding a larger sample size. The study is not powered to assess secondary clinical endpoints, however the sample size was calculated to be sufficient to provide relevant information about the role of an anti-inflammatory

therapy, colchicine, initiated early at diagnosis of AHF. Indeed, this is the larger study with an anti-inflammatory therapy in AHF, and, to our knowledge, there is only one ongoing trial testing colchicine in HF, albeit just HF with preserved LVEF and with an open-label design.³³ Another potential limitation is that the optimal duration of treatment with colchicine in AHF is unknown and the 8-week follow-up planned could be too short. Finally, it was not considered a personalized approach to identify patients who may get the greater benefit of an anti-inflammatory treatment,³⁴ but post-hoc analyses may be of additional value to explore this point.

Conclusion

The COLICA trial will be the first randomized double-blind placebo-controlled clinical trial testing colchicine for AHF. There is an unmet need for therapies in the acute phase of HF that may increase clinical stability and improve patient outcomes. Blocking the early acute inflammatory response with colchicine could be beneficial and become a new therapeutic option for HF.

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Appendix

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