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CLINICAL RESEARCH

Anti-Inflammatory Treatment With Colchicine in Stable Chronic Heart Failure

A Prospective, Randomized Study

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Objectives The purpose of this study was to test the efficacy of a 6-month course of anti-inflammatory treatment with colchicine in improving functional status of patients with stable chronic heart failure (CHF).

Background CHF has been shown to be associated with inflammatory activation. Inflammation has been designated as a therapeutic target in CHF.

Methods Patients with stable CHF were randomly assigned to colchicine (0.5 mg twice daily) or placebo for 6 months. The primary endpoint was the proportion of patients achieving at least one-grade improvement in New York Heart Association class.

Results Two hundred sixty-seven patients were available for final evaluation of the primary endpoint: its rate was 11% in the control group and 14% in the colchicine group (odds ratio: 1.40; 95% confidence interval: 0.67 to 2.93; $p = 0.365$). The rate of the composite of death or hospital stay for heart failure was 9.4% in the control group, compared with 10.1% in the colchicine group ($p = 0.839$). The changes in treadmill exercise time with treatment were insignificant and similar in the 2 groups ($p = 0.938$). C-reactive protein and interleukin-6 were both significantly reduced in the colchicine group (–5.1 mg/l and –4.8 pg/ml, respectively; $p < 0.001$ for both, compared with the control group).

Conclusions According to this prospective, randomized study, anti-inflammatory treatment with colchicine in patients with stable CHF, although effective in reducing inflammation biomarker levels, did not affect in any significant way patient functional status (in terms of New York Heart Association class and objective treadmill exercise tolerance) or the likelihood of death or hospital stay for heart failure. (J Am Coll Cardiol HF 2014;2:131–7) © 2014 by the American College of Cardiology Foundation

Activation of inflammatory mediators has long been suggested to contribute to the pathogenesis of the chronic heart failure (CHF) syndrome (1–3), and "inflammation," as a broad term involving a variety of mechanisms, has been implicated in a cross-talk of processes leading to fibrosis, enhanced apoptosis, and cellular dysfunction (4,5). The existing evidence has inevitably raised the question of targeting inflammation for therapeutic purposes in CHF, and a scientific statement on this issue has been published by a committee of the European Society of Cardiology (6).

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Although results from studies with the use of immunomodulatory agents for CHF (mainly targeting tumor necrosis factor) have been less than encouraging (7), interest in this line of research remains. Our group and others have studied colchicine, an agent with known potent anti-inflammatory action, in various clinical settings of cardiovascular disease, with positive initial results (8–11)

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Abbreviations and Acronyms

CHF = congestive heart failure

hsCRP = high-sensitivity C-reactive protein

IL = interleukin

NYHA = New York Heart Association

demonstrating a good safety profile of this drug at the studied doses.

In this theoretical and observational context, we sought to investigate whether a 6-month course of colchicine in patients with CHF would result in a significant improvement in functional and clinical parameters of heart failure.

Methods

Population. This was a single-center, prospective, double-blinded, placebo-controlled study. Patients with stable symptomatic heart failure and systolic left ventricular dysfunction (ejection fraction ≤40%) were included. Recently hospitalized patients (hospital stay for heart failure in the previous 3 months) were excluded. Other exclusion criteria were New York Heart Association (NYHA) class IV, recent (in the previous 6 months) implantation of a cardiac resynchronization treatment device, active inflammatory/infectious disease or malignancy, known autoimmune diseases, corticosteroid or other immunosuppressive or immunomodulatory therapy, moderate or severe hepatic impairment (Child-Pugh class B or C), severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2), current participation in another research protocol, and inability or unwillingness to adhere to standard treatment or to provide consent. The protocol was approved by the institutional review board. All patients provided informed consent.

Procedures. After a run-in period of 2 months, during which CHF treatment was optimized and stabilized, patients were re-evaluated for eligibility and entered the 6-month study treatment period. Clinical assessment was performed monthly during the treatment period, and complete transthoracic echocardiographic evaluation (including left ventricular ejection fraction assessment with the modified Simpson's rule) as well as a treadmill stress test (with the use of a modified Bruce protocol with 2 additional initial 3-min stages at 2.7 km/h, with 0% and 5% grade, respectively) were undertaken before and at the end of the study treatment period. Adjustments in CHF treatment were made according to patient status and standard clinical practice. B-type natriuretic peptide measurements were performed monthly and were taken into account to guide treatment. Blood samples for high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 measurement were obtained before and at the end of the treatment period. CRP and IL-6 were measured with the use of commercially available kits (R&D Systems, Minneapolis, Minnesota). All personnel involved in patient follow-up and evaluation were blinded as to the patients' random assignment.

Study treatments and adverse event monitoring. Patients were randomly assigned to receive colchicine or placebo for 6 months. Colchicine was administered at a dose of 0.5 mg twice daily. Patients with <60 kg body weight received 0.5 mg once daily. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, myotoxicity, and alopecia. To monitor potential subclinical organ toxicity, complete blood counts and standard biochemical analyses (glucose, urea, creatinine, liver enzymes, creatine kinase, and lactate dehydrogenase) were performed monthly.

Study endpoints. The primary study endpoint was the proportion of patients achieving at least one-grade improvement in NYHA functional status classification (NYHA class was determined by 2 independent blinded evaluators and in case of disagreement NYHA class was adjudicated by consensus with a third clinician). Secondary endpoints were the composite of death and hospital stay for CHF, change in left ventricular end-diastolic diameter, change in left ventricular ejection fraction, and change in treadmill exercise time over the 6-month treatment period.

Statistical analysis. It was calculated that to detect with a probability (power) of 90% a difference between the 2 treatment groups as to the primary endpoint, assuming a 25% rate in the active treatment group versus 10% in the placebo-treated patients, a sample size of 266 would be required in a 1:1 allocation scheme (at an alpha level of 0.05). Analysis was performed on an intention-to-treat basis (patients who received at least one dose of the study treatment were included). Continuous variables are expressed as mean ± SD and compared by use of the *t* test if their distribution did not deviate significantly from the Gaussian (tested with the Kolmogorov-Smirnov test). If significant deviation from the normal distribution was found, the corresponding parameters were summarized as medians and quartiles, and nonparametric tests (Wilcoxon's and Mann-Whitney) were used to confirm the results of parametric tests; however, because most of the studied variables did not deviate excessively from the normal distribution, all continuous variables are reported as mean ± SD, for reasons of uniformity of presentation. Categorical variables are expressed as percents and counts and compared by means of the chi-square test. Odds ratios were computed with the use of Mantel-Haenszel common odds estimates. Kaplan-Meier analysis was used to calculate mean free from hospital stay for heart failure survival, and the 2 groups were compared with the use of the log-rank test. The SPSS 17 software package was used (SPSS Inc., Chicago, Illinois). Two-sided p values of <0.05 were considered as indicative of statistical significance.

Results

Two hundred seventy-nine patients completed the run-in phase and entered the study treatment period (Fig. 1); nine died during the 6-month treatment and three were lost to follow-up. As a result, 267 patients were available for final evaluation of the primary endpoint. Baseline demographic and clinical characteristics are summarized in Table 1. The 2 treatment arms were well-balanced and equivalent in regard to important clinical and functional parameters. Of note, the

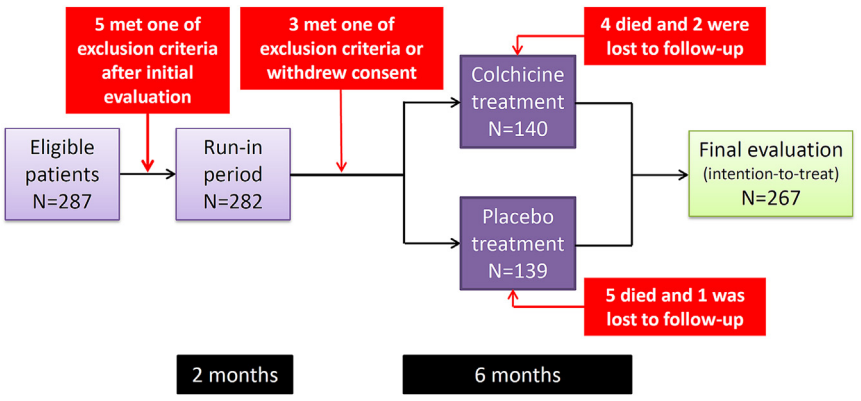

Figure 1 **Study Flow Chart**

Two hundred seventy-nine patients entered the study treatment period; 267 patients were available for evaluation of the primary endpoint at 6 months.

use of CHF medications that could act on the inflammatory status was balanced between the 2 groups at baseline (Table 1), and this picture was not altered until the end of the 6-month study-treatment period: statin use at 6 months was 71.4% versus 67.9% (p = 0.532) in the control group and colchicine group, respectively. The corresponding rates were 79.7% versus 80.6% (p = 0.854) for beta-blockers, 85.0% versus 85.8% (p = 0.843) for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 60.9% versus 61.9% (p = 0.862) for aldosterone antagonists.

Primary endpoint. The proportions of patients showing an improvement of at least one grade in NYHA functional

Table 1 **Baseline Patient Characteristics**

	Overall (n = 279)	Placebo Group (n = 139)	Colchicine Group (n = 140)	p Value
Age, yrs	66.7 ± 5.8	66.4 ± 5.7	66.9 ± 5.8	0.453
Male	187 (67%)	93 (67%)	94 (67%)	0.898
BMI, kg/m^2	25.9 ± 3.1	25.7 ± 3.0	26.1 ± 3.3	0.290
Hypertension	101 (36%)	53 (38%)	48 (34%)	0.532
Diabetes	48 (17%)	25 (18%)	23 (16%)	0.751
Dyslipidemia	91 (33%)	45 (32%)	46 (33%)	0.898
Ischemic CHF	198 (71%)	98 (71%)	100 (71%)	0.789
Nonischemic CHF	78 (28%)	40 (29%)	38 (27%)	0.789
DCM	24 (9%)	11 (8%)	13 (9%)	
Hypertensive	26 (9%)	14 (10%)	12 (9%)	
Valvular	19 (7%)	10 (7%)	9 (6%)	
Other	9 (3%)	5 (4%)	4 (3%)	
NYHA class	2.4 ± 0.5	2.4 ± 0.5	2.3 ± 0.5	0.530
Biventricular pacemaker	89 (32%)	43 (31%)	46 (33%)	0.699
Atrial fibrillation (permanent)	58 (21%)	27 (19%)	31 (22%)	0.555
LVEF, %	27.6 ± 4.3%	27.7 ± 4.3%	27.6 ± 4.4%	0.893
LVEDD, mm	61.9 ± 8.6	61.9 ± 9.0	61.9 ± 8.3	0.983
LVESD, mm	52.9 ± 8.1	53.0 ± 8.4	52.9 ± 7.8	0.191
TST time, min	11.1 ± 2.9	11.4 ± 3.0	10.9 ± 2.7	0.131
Treatment				
Beta-blocker	220 (79%)	110 (80%)	110 (79%)	1.000
ACEi/ARB	237 (85%)	117 (84%)	120 (86%)	0.604
ARA	172 (62%)	85 (61%)	87 (62%)	0.804
Statin	175 (63%)	86 (62%)	89 (64%)	0.708
Diuretic agent	191 (69%)	94 (68%)	97 (69%)	0.696

Values are mean ± SD or n (%).

ACEi = angiotensin-converting enzyme inhibitor; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; BMI = body mass index; CHF = chronic heart failure; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; TST = treadmill stress test.

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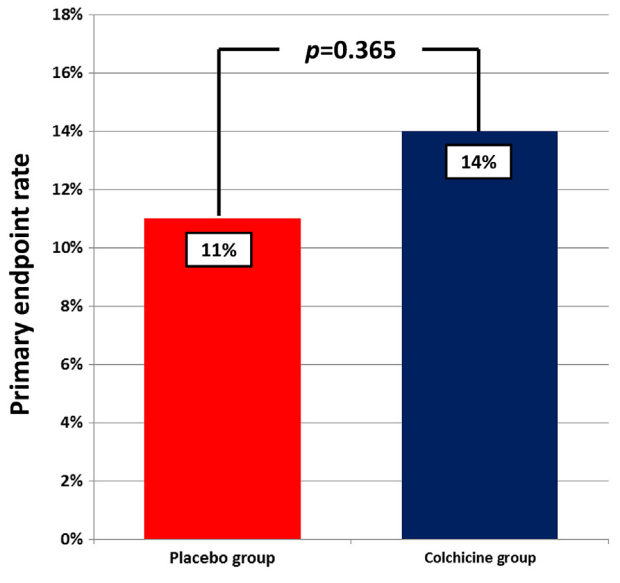

Figure 2 Primary Endpoint

Proportion of patients achieving at least one-grade improvement in New York Heart Association class at 6 months.

status class were equivalent in the 2 treatment arms (Fig. 2), which suggests a neutral effect of active treatment on patient functional status. The odds ratio for the colchicine-treated patients to meet the primary endpoint was 1.40 (95% confidence interval: 0.67 to 2.93; p = 0.365). Mean NYHA class at baseline was 2.4 ± 0.5 in the control group and 2.3 ± 0.5 in the colchicine group (p = 0.530). The corresponding values at the 6-month evaluation were 2.4 ± 0.7 and 2.3 ± 0.7 (p = 0.411), respectively. The mean change was 0.01 ± 0.62 in the control group and −0.01 ± 0.68 in the colchicine group (p = 0.707).

There were no significant interactions between the level of baseline inflammatory biomarker levels and the effectiveness of study treatment: the odds ratio for meeting the primary endpoint in patients with baseline hsCRP above the median treated with colchicine versus placebo was 1.31 (95% confidence interval: 0.46 to 3.74; p = 0.617) and the corresponding values for patients with baseline hsCRP below the median was 1.51 (95% confidence interval: 0.54 to 4.23; p = 0.438).

In a per-protocol analysis, excluding patients who discontinued treatment (instead of the prespecified intention-to-treat analysis), the primary endpoint rate was 13.9% in the colchicine group and 10.1% in the control group (p = 0.346), with an estimated odds ratio of 1.45 (95% confidence interval: 0.67 to 3.12).

Secondary endpoint. Overall, 27 patients (9.8%) died (n = 9) or were hospitalized for CHF (n = 22) during the 6-month treatment period. The rate of this composite endpoint was 9.4% in the control group, compared with 10.1% in the colchicine group (odds ratio: 1.09; 95% confidence interval: 0.49 to 2.40; p = 0.839). The Kaplan-Meier mean hospital stay-free survival time was 24.8 weeks (95% confidence interval: 24.1 to 25.5) in the control group compared with 24.7 weeks in the colchicine group (95% confidence interval: 24.0 to 25.5) (Fig. 3).

Among the secondary echocardiographic endpoints, changes over the treatment period were minimal overall. Left ventricular dimension changes showed minor albeit statistically significant differences between the 2 groups (Table 2). In particular, colchicine was associated with a decrease in both end-diastolic and end-systolic left ventricular diameters; however, it can readily be appreciated from

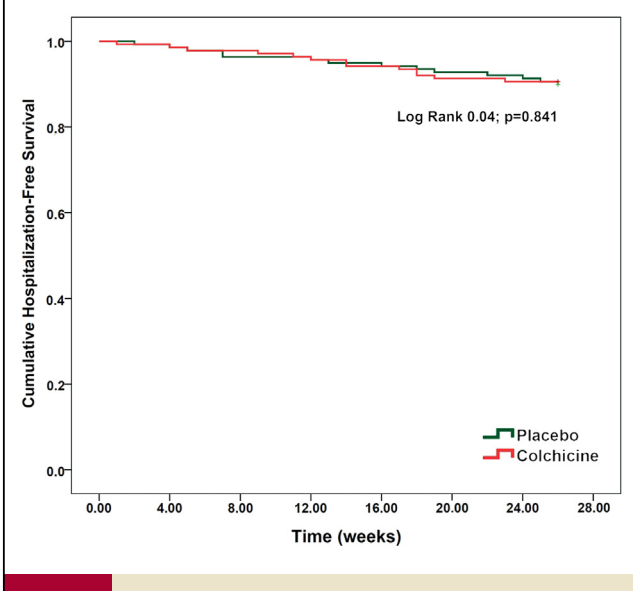

Figure 3 Death or Hospital Stay for Heart Failure

Kaplan-Meier curves of the secondary composite endpoint in the 2 treatment arms.

Table 2 Changes in Functional and Structural Parameters

	Placebo Group (n = 133)	Colchicine Group (n = 134)	p Value
LVEF pre-treatment, %	27.8 ± 4.3	27.8 ± 4.3	0.915
LVEF post-treatment, %	27.1 ± 5.7	27.8 ± 6.0	0.335
Δ(LVEF), %	−0.7%	0.0%	0.119
LVEDD pre-treatment, mm	61.7 ± 8.9	61.7 ± 8.3	0.987
LVEDD post-treatment, mm	61.9 ± 8.9	60.9 ± 8.4	0.350
Δ(LVEDD), mm	0.3	−0.8	<0.001
LVESD pre-treatment, mm	52.7 ± 8.3	52.7 ± 7.8	0.941
LVESD post-treatment, mm	53.2 ± 8.6	52.1 ± 7.8	0.305
Δ(LVESD), mm	0.4	−0.5	<0.001
TST time pre-treatment, min	11.5 ± 3.0	10.9 ± 3.3	0.120
TST time post-treatment, min	11.5 ± 3.2	10.9 ± 2.6	0.169
Δ(TST time), min	−0.1	−0.1	0.938

Values are mean ± SD unless otherwise indicated. Δ denotes change (post-treatment minus pre-treatment values).

Abbreviations as in Table 1.

the data of Table 2 that the effect sizes were very small (in the order of tenths of a millimeter). Exercise time in the modified Bruce protocol treadmill test, on the other hand, was similar in the 2 groups.

Inflammation markers. Colchicine treatment was associated with marked decrease in the measured inflammatory biomarkers over the study treatment period. The magnitude of reduction was significantly higher in the colchicine group compared with that in the control group for hsCRP and IL-6 (Fig. 4).

Safety aspects and discontinuations. The main symptoms associated with colchicine use were, as expected, gastrointestinal, with 18.7% of patients in the colchicine group reporting diarrhea, versus 7.5% of control subjects ($p = 0.007$). No serious complications in terms of renal and hepatic function were observed: the proportion of patients with a 10% or higher reduction in estimated glomerular filtration rate during the 6-month study treatment was 13.4% in the colchicine group compared with 14.1% in control subjects ($p = 0.605$), whereas three cases of liver function test elevation (above 3 times the upper limit of normal) were observed (2 in the colchicine group and 1 control subject), which were all self-limiting without clinical consequences. No cases of myotoxicity or myelotoxicity were reported. The discontinuation rate was 9.0% in the colchicine group and 3.0% in the placebo group ($p = 0.041$).

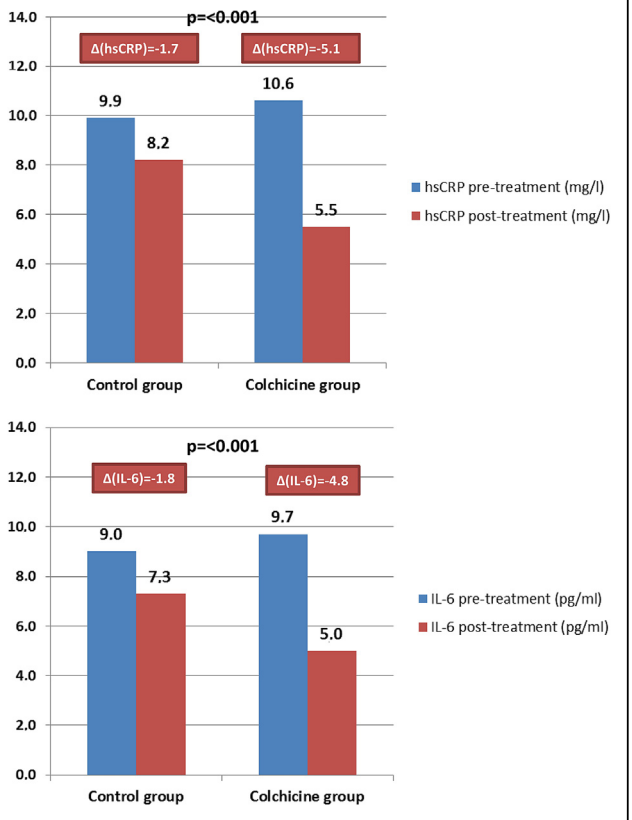

Figure 4 Levels of Inflammation Biomarkers

Change of mean levels of serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 over the 6-month treatment period in each treatment group. Δ denotes change. The p values correspond to the comparison of changes between groups.

Discussion

According to the results of this prospective, randomized study, anti-inflammatory treatment with colchicine in patients with stable CHF, although effective in reducing inflammatory biomarker levels, does not affect in any significant way patient functional status (in terms of NYHA class or objective exercise tolerance). A minimal favorable effect of treatment on left ventricular dimensions was observed, but this was not translated into functional improvement. In terms of cardiovascular safety of the studied treatment, the evidence suggests that colchicine, in the relatively low doses used in this study, is safe for administration to patients with CHF, as opposed to other classes of anti-inflammatory agents. It can be deduced that although colchicine reduces pro-inflammatory activation in CHF, it is of meager—if any—clinical benefit, at least in the time frame and patient population studied in the present trial. Of note, the primary endpoint of the study was chosen to be quite conservative (the sample size was calculated on the assumption that at least 25% of patients in the colchicine group would achieve one-grade improvement in NYHA class); therefore, failure to observe an effect of treatment on this conservative outcome measure implies that there is indeed lack of efficacy of colchicine in this clinical setting.

The pathogenetic link between inflammatory processes and CHF has been actively researched in the past with an initial focus on cytokines (2,3), followed by other pro-inflammatory pathways (12–18). This has led to a number of clinical studies studying the potential of anti-inflammatory and immunomodulatory agents to influence the course of heart failure (7,19–21). The results of these trials have been either neutral or negative (even suggesting harm in CHF), with the exception of preliminary data for the potential role of interleukin-1 inhibition for the prevention of heart failure after an acute myocardial infarction (21,22).

A common characteristic of the agents used in the previously-mentioned trials is that they are novel biological therapies, at the edge of new drug research, targeting specific molecules of the inflammatory cascade. Colchicine, on the other hand, is an old, quite inexpensive drug whose main mechanism of action involves inhibition of microtubule polymerization by binding to β-tubulin, thus affecting any process that requires cytoskeletal changes, including cell mitosis, exocytosis, and neutrophil motility (23,24). An important aspect of the observed effects of colchicine, partly explaining its potent anti-inflammatory action, is the fact that it readily enters leukocytes, where it remains in much higher concentrations than plasma (25). Colchicine can be found inside leukocytes for up to several days after

administration (26), with this local pooling and long half-life explaining why a once- or twice-daily dose is enough to suppress inflammation. The effectiveness of colchicine in suppressing inflammation was amply demonstrated in the population of the present study by the marked decreases in inflammatory biomarkers, namely hsCRP and IL-6 in the active treatment arm.

There is, as a result, no doubt that colchicine (just like the immunomodulatory agents used in other studies of CHF) can indeed suppress pro-inflammatory activation in patients with CHF, but this effect does not appear to lead to any discernible clinical benefit. There are a number of plausible reasons for these observations. Inflammation in CHF may be an epiphenomenon or rather a manifestation of underlying mechanisms leading to the chronic clinical deterioration, which is characteristic of this syndrome. In that case, fighting inflammation is something like "killing the messenger": it will have no effect on the processes fueling myocardial dysfunction and systemic sequelae of heart failure. Another potential explanation is that the studied immunomodulatory agents inhibit a specific step of the inflammatory cascades, whereas inflammatory processes can continue by way of other pathways. There is also the issue of potential adverse effects of these agents: inhibiting a pro-inflammatory mediator may be accompanied by other—potentially unknown—effects, with unfavorable results on heart failure.

Finally, another useful result of the present study is the demonstration of safety of this dose of colchicine in patients with CHF, as evidenced not only by the close adverse event monitoring but also by the secondary efficacy/safety composite endpoint of death/hospital stay for heart failure. These findings are reassuring for patients with CHF who need treatment with colchicine for traditional indications (e.g., gouty arthritis, pericarditis, and so on) in which options for safe anti-inflammatory therapy are in short supply, given the known unfavorable cardiovascular safety profile of steroid and non-steroid anti-inflammatory drugs, especially for patients with CHF.

Study limitations. The general term "heart failure" encompasses a variety of manifestations of this syndrome, with different pathophysiological substrates; this means that the results obtained in a certain heart failure population cannot be extrapolated with ease to other heart failure patient subsets. Furthermore, it could be argued that the primary endpoint of this study is a "soft" endpoint, amenable to subjective interpretation of patient status by the evaluators. However, it should be noted that NYHA classification has been extensively validated in clinical trials as a prognostic indicator and, in addition, the results of the NYHA class evaluation in this study were reiterated by an objectively assessed functional measure, namely treadmill exercise time. In any case, the choice of a functional status outcome instead of a hard clinical endpoint should have favored the demonstration of effectiveness of the studied intervention. Another point of criticism for the choice of primary endpoint could be that the involved outcomes may not be homogeneous: an improvement from class III to class II might be more or less difficult than improvement from class II to class I. However, even if such a discrepancy did exist, it would be equivalent in the 2 study treatment arms, which included similar proportions of NYHA classes. Furthermore, no imbalance was observed between the 2 groups regarding the proportion of improvement from class III to II versus II to I.

Conclusions

A 6-month course of colchicine in patients with stable CHF, despite suppressing the levels of inflammatory biomarkers and exhibiting a good safety profile, did not lead to improvement in any of the studied descriptors of patient functional status and had a neutral effect on the rate of death or hospital stay for heart failure.

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REFERENCES

1. Mann DL, Young JB. Basic mechanisms in congestive heart failure: recognizing the role of proinflammatory cytokines. Chest 1994;105:897–904.
2. Rauchhaus M, Doehner W, Francis DP, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060–7.
3. Deswal A, Petersen NJ, Feldman AM, et al. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation 2001;103:2055–9.
4. Mann DL. Targeted anticytokine therapy and the failing heart. Am J Cardiol 2005;95:9C–16C.
5. Hofmann U, Frantz S. How can we cure a heart "in flame"? A translational view on inflammation in heart failure. Basic Res Cardiol 2013;108:356.
6. Heymans S, Hirsch E, Anker SD, et al. Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2009;11:119–29.
7. Gullestad L, Aukrust P. Review of trials in chronic heart failure showing broad-spectrum anti-inflammatory approaches. Am J Cardiol 2005;95:17C–23C.
8. Deftereos S, Giannopoulos G, Raisakis K, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol 2013;61:1679–85.
9. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol 2012;60:1790–6.
10. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013;61:404–10.
11. Imazio M, Brucato A, Ferrazzi P, et al., COPPS Investigators. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation 2011;124:2290–5.
12. Crackower MA, Oudit GY, Kozieradzki I, et al. Regulation of myocardial contractility and cell size by distinct PI3K-PTEN signaling pathways. Cell 2002;110:737–49.

13. Patrucco E, Notte A, Barberis L, et al. PI3K gamma modulates the cardiac response to chronic pressure overload by distinct kinase-dependent and -independent effects. Cell 2004;118:375–87.
14. Weber KT. Extracellular matrix remodeling in heart failure: a role for de novo angiotensin II generation. Circulation 1997;96:4065–82.
15. Hudson MP, Armstrong PW, Ruzyllo W, et al. Effects of selective matrix metalloproteinase inhibitor (PG-116800) to prevent ventricular remodeling after myocardial infarction: results of the PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial. J Am Coll Cardiol 2006;48:15–20.
16. Schellings MWM, Pinto YM, Heymans S. Matricellular proteins in the heart: possible role during stress and remodeling. Cardiovasc Res 2004;64:24–31.
17. Schroen B, Heymans S, Sharma U, et al. Thrombospondin-2 is essential for myocardial matrix integrity: increased expression identifies failure-prone cardiac hypertrophy. Circ Res 2004;95:515–22.
18. Van Tassell BW, Arena RA, Toldo S, et al. Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure. PLoS One 2012;7:e33438.
19. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
20. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
21. Abbate A, Kontos MC, Grizzard JD, et al., VCU-ART Investigators. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study). Am J Cardiol 2010;105:1371–7.
22. Abbate A, Van Tassell BW, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study]. Am J Cardiol 2013;111:1394–400.
23. Terkeltaub RA. Colchicine update: 2008. Semin Arthritis Rheum 2009;38:411–9.
24. Deftereos S, Giannopoulos G, Papoutsidakis N, et al. Colchicine and the heart: pushing the envelope. J Am Coll Cardiol 2013;62:1817–25.
25. Sabouraud A, Chappey O, Dupin T, Scherrmann JM. Binding of colchicine and thiocolchicoside to human serum proteins and blood cells. Int J Clin Pharmacol Ther 1994;32:429–32.
26. Chappey ON, Niel E, Wautier JL, et al. Colchicine disposition in human leukocytes after single and multiple oral administration. Clin Pharmacol Ther 1993;54:360–7.

Key Words: colchicine ▪ C-reactive protein ▪ heart failure ▪ inflammation ▪ interleukin-6.