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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