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EDITORIAL COMMENT

Colchicine and the Failing Heart

A "FINER" Anti-Inflammatory Agent?*

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Ever since the original description of proinflammatory cytokines in patients with heart failure in 1990 (1), there has been enormous interest in the role that these molecules play in regulating cardiac structure and function, particularly with regard to their potential role in disease progression in heart failure. The recognition of the important pathophysiological consequences of sustained expression of proinflammatory mediators in pre-clinical and clinical heart failure models culminated in a series of multicenter clinical trials that utilized "targeted" approaches to neutralize tumor necrosis factor in patients with moderate to advanced heart failure. Unfortunately, these targeted approaches were negative with respect to the primary endpoints of the trial and, in some patients, resulted in worsening heart failure and/or death (2,3). Collectively, these 2 clinical trials have had a chilling effect on further attempts to target inflammation in heart failure, and have raised a number of nagging questions about what role, if any, proinflammatory cytokines play in the pathogenesis of heart failure. Germane to the present discussion, in this issue of *JACC: Heart Failure*, Deftereos et al. (4) report their findings on a 6-month course of treatment with colchicine in patients with heart failure

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with a depressed ejection fraction ≤40%. The rationale for this study was that colchicine has been known to exert anti-inflammatory effects in various cardiovascular settings (5), and might therefore also be useful in treating heart failure patients. Patients with stable heart failure on appropriate medical therapy were randomized to receive colchicine (0.5 mg twice daily) or placebo for 6 months. The primary endpoint of the study, for which the trial was powered adequately, was the proportion of patients achieving at least a 1-grade improvement in New York Heart Association functional class. Secondary endpoints, for which the trial was not adequately powered for, included a composite of death and hospital stay for heart failure, the change in left ventricular and end-diastolic diameter (2-dimensional echocardiography), change in left ventricular ejection fraction, and change in treadmill exercise time. In comparison to patients who were treated with conventional heart failure therapy, the authors observed that 11% of the control subjects had an improvement in New York Heart Association functional class, whereas 14% of patients in the colchicine group experienced an improvement in New York Heart Association functional classification ($p = 0.36$). Moreover, 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 ($p = 0.84$). The changes in treadmill exercise time were insignificant in the control group and treatment arms. Importantly, the magnitude of the decrease in circulating levels of C-reactive protein (CRP) and interleukin (IL)-6 were both significantly reduced in the colchicine-treated group when compared with placebo. There was an approximately 2-fold increase ($p = 0.007$) in gastrointestinal symptoms in the treatment group, whereas there were no serious complications in terms of renal and/or hepatic function. The authors conclude that anti-inflammatory treatment with colchicine in patients with stable heart failure, although effective in reducing inflammation biomarker levels, did not significantly affect functional class or the likelihood of death or hospital stay. Given the negative outcome of previous trials using anti-inflammatory agents in heart failure, the current study raises further questions about targeting of inflammation in this patient population.

Colchicine as an Anti-Inflammatory Agent in Heart Failure

Before addressing the clinical significance of the study by Deftereos et al. (4), it is useful to digress for a moment to discuss the biological plausibility of the use of colchicine in this patient group. In 2007, Hulley et al. (6) suggested the use of the "FINER criteria" for developing a research plan. As shown in Table 1, the FINER criteria highlight several useful points that increase the likelihood of developing a successful research plan. Notably, the study by Deftereos et al. (4) meets many, but not all of the FINER criteria outlined by Hulley et al. (6). Based on prior studies in the data that have suggested a role for colchicine in pericarditis, atrial fibrillation, and acute coronary syndromes, the current study meets the criteria of being feasible, interesting, novel, and ethical. However, the broader issue of whether this study is relevant to the existing scientific knowledge base regarding inflammation in heart failure is not at all clear, as will be discussed in the following text.

Colchicine has been used for centuries as an anti-inflammatory agent for acute gouty arthritis, and it is

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Table 1 FINER Criteria for a Good Research Question

Feasible	Adequate number of subjects Adequate technical expertise Affordable in time and money Manageable in scope
Interesting	Getting the answer intrigues investigator, peers, and community
Novel	Confirms, refutes, or extends previous findings
Ethical	Amenable to a study that institutional review board will approve
Relevant	To scientific knowledge To clinical and health policy To future research

Data from Hulley et al. (6).

currently approved by the U.S. Food and Drug Administration for the treatment of familial Mediterranean fever and as a prophylaxis against gout. However, it has not been until recently that colchicine has been considered as a second-line treatment for other cardiovascular conditions such as acute pericarditis, atrial fibrillation, and acute coronary syndromes (5). Colchicine binds to unpolymerized tubulin heterodimers to form a stable complex that effectively inhibits microtubule dynamics, thus affecting any process that requires cytoskeletal changes, including cell mitosis and exocytosis. Apart from inhibiting mitosis, colchicine also inhibits neutrophil motility and activity, thereby leading to a net anti-inflammatory effect. Colchicine also appears to block crystal-induced activation of the NLRP3 inflammasome, which leads to the processing of mature interleukin-1β and -18. Of note, it has been postulated that microtubule abundance can impede myocardial contractility, particularly in pressure overload models of cardiac hypertrophy (7). However, the applicability of these findings to heart failure has been challenged by other experimental studies, which have shown that colchicine-induced improvements in contractility in experimental models are model dependent (8). Although colchicine is known to have a large volume of distribution in normal subjects, the absorption, volume of distribution, and clearance of colchicine in heart failure are not known. In this regard, the dosing strategy in the present study of 0.5 mg colchicine twice daily was appropriately conservative, given the lack of pharmacokinetic and pharmacodynamic information about colchicine in a heart failure population. Nonetheless, it bears emphasis that there is no information with respect to whether the dose and/or dosing strategy of colchicine used in this study was sufficient to achieve known effective steady-state plasma concentrations of colchicine.

Apart from the issues regarding effective dose and dosing of colchicine in heart failure patients, the rationale for using this agent to target inflammation in heart failure patients is unclear based on the postulated mechanism(s) of increased inflammation in heart failure, which include activation and release of proinflammatory cytokines by the heart and/or immune system following tissue injury, elaboration of proinflammatory cytokines secondary to underperfusion of systemic tissues, increased levels of circulating endotoxin (a known pro-inflammatory stimulus) secondary to bowl edema, and/or persistent neurohormonal activation that triggers increased activation of pro-inflammatory cytokines in the heart and/or peripheral circulation. Based on the known mechanism of action of colchicine, it is unclear whether this alkaloid targeted any of the potential inflammatory pathways that have been identified in heart failure. Although the study by Deftereos et al. (4) reported that the magnitude of the decrease in the concentration of circulating levels of CRP and IL-6 was greater in colchicine-treated heart failure patients relative to controls, similar decreases in CRP and IL-6 levels were also observed in the control group. Unfortunately, the authors did not specify whether the decreases in CRP and IL-6 levels in the control group were also statistically significant, which makes it difficult to interpret the clinical significance of the decrease in inflammatory biomarkers in the colchicine group, insofar as there is no information on whether the magnitude of the small but statistically-significant differences in circulating inflammatory biomarkers are important biologically and/or clinically.

Conclusions: Is Colchicine in Heart Failure a FINER Anti-Inflammatory Agent?

The study by Deftereos et al. (4) is a small, prospective, randomized clinical trial that shows that conservative doses of a nonspecific anti-inflammatory agent have no effect on patient functional status in chronic heart failure. Based on the foregoing discussion regarding the dose and dosing of colchicine in heart failure and the absence of a defined mechanism of action for colchicine in heart failure, these neutral findings are perhaps not at all surprising. This statement notwithstanding, healthcare providers should be reassured that the dose of colchicine used in the present can be used safely in heart failure patients who have gouty arthritis or pericarditis. Unfortunately, from a scientific stand point we probably have not learned anything new about targeting inflammation in heart failure.

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