Review Article

Cardiovasc Prev Pharmacother 2022;4(1):7-12
eISSN 2671-700X
https://doi.org/10.36011/cpp.2022.4.e5

Cardiovascular Prevention and Pharmacotherapy

Anti-inflammatory effects of colchicine on coronary artery disease

Hun-Jun Park

Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Inflammation plays a crucial role in the pathophysiology of coronary artery disease (CAD). Several types of sterile inflammation are mediated through the nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 (NLRP3) inflammasome. Colchicine has recently been shown to effectively block NLRP3 inflammasome assembly in addition to several other actions on inflammatory cells. Recent evidence also points to favorable effects of colchicine in patients with CAD, including lower levels of inflammatory markers, coronary plaque stabilization, and more favorable cardiac recovery after injury. This review focuses on the role of colchicine in the process of atherosclerosis and discusses its potential as a therapeutic option for the prevention and treatment of CAD.

Keywords: Atherosclerosis; Inflammation; Interleukin-1; Colchicine; Coronary artery disease

INTRODUCTION

Despite significant advances in our understanding and treatment of atherosclerosis, its clinical manifestation of coronary artery disease (CAD) remains the leading global cause of death worldwide [1]. Even with optimal treatment, there is still a significant incidence of cardiovascular (CV) events, as up to 20% of patients with acute coronary syndrome (ACS) have a recurrent major adverse cardiovascular event in the first 3 years [2]. Therefore, more effective and widely available therapies are needed to further reduce the risk of CV events and mortality.

Inflammation plays a crucial role in the pathogenesis of atherosclerotic plaque development, progression, and rupture, and elevated levels of inflammatory markers have been shown to be predictive of future CV events [3]. The specific targeting of these processes in experimental models has been shown to attenuate myocardial and arterial injury, reduce disease progression, and promote healing. However, there have been few attempts to examine the potential role of anti- inflammatory treatment in this setting, possibly because attempts to translate these treatments into clinical practice and demonstrate clear efficacy have yielded disappointing results [4].

Recent evidence indicates that several types of sterile inflammation are mediated through the nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 (NLRP3) inflammasome. This inflammasome regulates caspase-1 activation and the subsequent processing of the potent inflammatory cytokine interleukin (IL)-1β,

Received: December 29, 2021; **Revised:** January 9, 2022; **Accepted:** January 18, 2022
Correspondence to Hun-Jun Park, MD, PhD
Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea. E-mail: cardioman@catholic.ac.kr

as well as triggering inflammatory cell death pyroptosis [5]. Inhibition of the NLRP3 inflammasome and its downstream inflammatory cytokines improved outcomes in patients with CAD. The recent phase III Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial revealed the efficacy of IL-1β inhibition by canakinumab in preventing recurrent CV events in patients with myocardial infarction (MI) [6]. However, because of the expensive cost and the need to administer the drug on an ongoing basis, it is unlikely that canakinumab will be widely used for the prevention of recurrent MI.

Colchicine is a widely available, safe, and low-cost drug primarily used for the treatment of gout and familial Mediterranean fever. In the cardiology field, it is widely employed as an anti-inflammatory agent for acute and recurrent pericarditis [7]. Colchicine has recently been shown to effectively block NLRP3 inflammasome assembly in addition to several other actions on inflammatory cells [8]. Recent evidence also points to favorable effects of colchicine in patients with CAD, including lower levels of inflammatory markers, coronary plaque stabilization, and more favorable cardiac recovery after injury [9]. Therefore, this review focuses on the role of colchicine in the process of atherosclerosis and discusses its potential as a therapeutic target for the prevention and treatment of CAD.

INFLAMMATION AND PATHOPHYSIOLOGY OF CAD

Monocytes/macrophages and neutrophils are key effectors of the inflammatory response present throughout the entire atherosclerotic process, and they closely interact mutually to enhance their activity through the activation of the NLRP3 inflammasome [10]. During the early phases, endothelial cell adhesion molecules drive the recruitment of monocytes, followed by chemokine-guided migration into the arterial intima [11]. Thereafter, multiple signals determine the maturation of these cells into macrophages, which engulf oxidized low-density lipoprotein and cholesterol crystals, inducing the release of several cytokines, most importantly IL-1β and tumor necrosis factor (TNF)-α, and resulting in their transformation into foam cells and activation of the NLRP3 inflammasome [12]. This results in a burst response of proinflammatory mediators activating the endothelium, leading to the further recruitment of leukocytes and perpetuation of the inflammatory microenvironment [13].

Neutrophils are also important drivers of the innate immune response in atherogenesis and plaque rupture. They accumulate in the shoulder regions of plaques, the area most prone to rupture, and release metalloproteinases, which are known to degrade the constituents of the fibrous cap [14]. They also secrete elastase, which is capable of cleaving almost all components of the extracellular matrix, as well as inducing further chemotaxis secondary to ligand exposure [15]. Myeloperoxidase can produce reactive oxygen species and promote lipid peroxidation, resulting in endothelial dysfunction by nitric oxide depletion [16]. Neutrophils can prime macrophages to produce pro-IL-1β, which later is transformed into its mature form, IL-1β, through NLRP3 inflammasome activation, further aggravating the inflammatory cascade [17].

ANTI-INFLAMMATORY EFFECTS OF COLCHICINE

Microtubules in neutrophils

Colchicine is unique in that its mechanism of action does not involve the arachidonic acid pathway, which is affected by non-steroidal anti-inflammatory drugs and glucocorticosteroids. Colchicine irreversibly intercalates into free α/β-tubulin dimers that incorporate into and block microtubule extension [18]. During inflammation, microtubules facilitate the movement of adhesion molecules onto cell surfaces. Colchicine concentrations are much higher in neutrophils than in other leukocytes due to the diminished activity of the P-glycoprotein membrane efflux pump, which serves as an energy-dependent colchicine efflux transporter [19]. Thus, even at low doses, it impairs adhesion of neutrophils to the endothelium by reducing both E- and P-selectin expression, inhibiting neutrophil migration, and thereby attenuating inflammation [20]. The disruption of microtubules also diminishes the rheologic capacity of neutrophils, inhibiting their transmigration out of blood vessels [21]. Although the mechanisms are less well understood, colchicine interferes with several steps in the inflammatory process by inhibiting the synthesis of TNF-α, leukotriene B4, prostaglandin E2 and TxA2, as well as the activity of cyclooxygenase-2 [22]. It also inhibits neutrophil release of α-defensin and diminishes neutrophil-to-platelet aggregation, thereby potentially preventing large thrombus burdens [23].

NLRP3 inflammasome in monocytes/macrophages and neutrophils

The innate immune response relies on pattern-recognition receptors to target pathogenic or dangerous signals. Inflammasomes are cytoplasmic pattern-recognition receptors, of which the best characterized is NLRP3 [24]. Colchicine has recently been shown to decrease IL-1β and IL-18 production by blocking the activity of the NLRP3 inflammasome. Two studies confirmed the inhibitory activity of colchicine at the NLRP3 inflammasome. In patients with ACS, in whom acute colchicine administration (1 mg followed by 0.5 mg within 24 hours before sampling) resulted in a significantly lower transcoronary release of these cytokines. The transcoronary cytokine levels of ACS colchicine-treated patients were notably similar to those of patients with no obstructive CAD [25]. The local reduction in IL-1β and IL-18 levels were highly suggestive of NLRP3 inflammasome inhibition. This was later confirmed in a follow-up study using stimulated peripheral monocytes from patients from a different cohort with ACS, where short-term colchicine administration resulted in a significant reduction of both intracellular and secreted IL-1β, via inhibition of inflammasome caspase-1 [26]. There are several mechanisms of action by which colchicine can suppress NLRP3 inflammasome activation: (1) inhibition of the expression of the pyrin domain, (2) prevention of intracellular transport of mitochondrial-associated apoptosis-associated speck-like protein containing a caspase recruitment domain to NLRP3, (3) inhibition of protein expression of cleaved caspase-1, and (4) inhibition of P2X7-mediated K^+ efflux. The final process is the inhibition of the active form of IL-1β and IL-18 production and the recruitment of additional neutrophils and macrophages [8].

CLINICAL APPLICATIONS OF COLCHICINE ON CAD

Atherosclerosis and plaque vulnerability

There has been recent interest in using low-dose colchicine to treat the chronic inflammation associated with atherosclerotic disease. The reduction in inflammatory biomarkers seems to be related to atherosclerotic plaque modification into a more stable phenotype. In a prospective, non-randomized study of 80 patients with recent ACS, 0.4 mg of colchicine daily plus optimal medical therapy resulted in a significant reduction of low-attenuation plaque volume seen on computed tomography coronary angiography (15.9 mm^3 [–40.9%] vs. 6.6 mm^3 [–17.0%]; P=0.008) and high-sensitivity C-reactive protein (mean, 1.10 mg/L [–37.3%] vs. 0.38 mg/L [–14.6%]; P<0.001). This change in low-attenuation plaque was positively associated with a reduction in high-sensitivity C-reactive protein levels in patients receiving colchicine (r=0.578, P<0.001) [27]. These favorable effects seem to be correlated with clinical benefits. In a retrospective study of 1288 gout patients, the prevalence of MI was 1.2% in colchicine users versus 2.6% in no-colchicine users (P=0.03). Colchicine users also had fewer deaths and lower C-reactive protein levels, although these did not achieve statistical significance [28]. According to a Cochrane meta-analysis including 39 randomized controlled trials with 4,992 patients receiving colchicine for multiple indications, colchicine may have substantial CV benefits, especially for the reduction of CV mortality and MI [29].

Colchicine's activity in atherosclerosis was first examined in stable CAD. Colchicine (0.5 mg twice daily) was associated with a 60% relative reduction in C-reactive protein levels in patients with stable CAD on high-intensity atorvastatin therapy at baseline. This suggests that colchicine may have additive effects to statin therapy for reducing C-reactive protein levels [30]. In an earlier open-label trial of low-dose colchicine (LoDoCo) involving 532 patients with chronic CAD, treatment with colchicine (0.5 mg daily) was associated with a 67% relative risk reduction in acute CV events over 3 years, suggesting a potential role of colchicine on plaque stabilization [31]. A subsequent randomized double-blind trial involving 5,522 patients with chronic CAD after at least 6 months of a clinically stable condition (LoDoCo2) showed that low-dose colchicine prevented acute CV events, including CV death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization, which occurred at a 31% lower rate than in those who received placebo [32].

ACS is associated with higher risks of recurrent events and exacerbated inflammation. In a randomized double-blind trial involving 4,745 patients within a month after MI (Colchicine Cardiovascular Outcomes Trial [COLCOT]), the risk of acute CV events was also 23% lower in those who received low-dose colchicine (0.5 mg once daily) than those who received placebo. This result was due predominantly

to a lower incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization [33]. These benefits of colchicine with regards to CV events in COLCOT were at least as large as those of canakinumab in CANTOS.

However, there were no benefits in the Australian COPS (Colchicine in Patients With Acute Coronary Syndrome) Trial regarding the composite endpoint of all-cause mortality, ACS, ischemia-driven urgent revascularization, or non-cardioembolic ischemic stroke in 396 patients, who were randomized to colchicine (0.5 mg twice daily) for 30 days followed by 11 months of colchicine at a dose of 0.5 mg daily, compared with 399 patients randomized to placebo. There was a higher rate of total death (8 vs. 1; P=0.017, log-rank), particularly non-CV death, in the colchicine group (5 vs. 0; P=0.024, log-rank). However, this trial was underpowered to detect between-group differences with such a low event rate, and therefore these results must be interpreted with caution [34].

Infarct size after short-term colchicine treatment

After ST-elevation MI (STEMI), an important inflammatory response starts in the minutes after reperfusion and peaks in the first days after reperfusion. Over the past years, a substantial volume of evidence has identified that inflammatory cells such as neutrophils, followed by monocytes and macrophages, rapidly infiltrate the injured myocardium with abundant proinflammatory cytokine secretions that may cause additional damage to the myocardium in patients presenting with STEMI [4,35].

Deftereos et al. [36] conducted a double-blind, placebo-controlled trial to determine whether a 5-day course of colchicine could reduce infarct size in 151 STEMI patients after percutaneous coronary intervention. Infarct size was measured by the surrogate endpoints of CK-MB fraction concentration and troponin T. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement was used in a subset of 60 patients to measure infarct volume. Patients were randomized 1:1 to colchicine with a 2-mg loading dose followed by 0.5 mg twice daily or to placebo for 5 days. The 72-hour median area under the curve of CK-MB and peak troponin T was significantly reduced in patients receiving colchicine compared with placebo. There was a significant reduction in infarct volume as seen on cardiac MRI (median, 18.8 mL; interquartile range, 8.1–28.5 mL vs. median, 25.1 mL; interquartile range, 20.0–35.9 mL; P=0.019).

On the contrary, the COVERT-MI investigators randomly assigned 192 STEMI patients referred for primary percutaneous coronary intervention to receive oral colchicine (2-mg loading dose followed by 0.5 mg twice a day, n=101) or matching placebo (n=91) from admission to day 5. At 5 days, the gadolinium enhancement-defined infarct size did not differ significantly between the colchicine and placebo groups (P=0.87). At 3 months of follow-up, there were no significant differences in infarct size and left ventricular remodeling between the colchicine and placebo groups [37]. This discrepancy between these studies may be related to differences in study design. This former study assessed infarct size reduction by using myocardial biomarker release and only reported infarct size reduction on cardiac MRI in a subgroup of patients. The latter trial used an accepted primary endpoint with core laboratory measurement of cardiac MRI infarct size.

Cardiac remodeling after long-term colchicine treatment

Inflammation has long been suggested to contribute to cardiac remodeling through crosstalk of inflammatory mediators, leading to chronic heart failure (CHF) by fibrosis, enhanced apoptosis, and cellular dysfunction. This has led to a number of clinical studies studying the potential of anti-inflammatory and immunomodulatory agents to influence the course of CHF. In a placebo-controlled trial of anakinra (an IL-1 receptor antagonist) in patients with MI, a 14-day course of anakinra treatment showed a beneficial effect on left ventricular end-systolic volume index compared to patients given a placebo, which is likely to have been due to a reduction in cardiac remodeling that takes place after the loss of viable heart muscle, resulting in CHF [38,39].

In contrast, Deftereos et al. [40] studied colchicine, an agent with known potent anti-inflammatory action, in 267 patients with stable symptomatic heart failure and systolic left ventricular dysfunction (ejection fraction ≤40%). This prospective, randomized study showed that a 6-month course of colchicine (0.5 mg twice daily) in patients with stable CHF, although effective in reducing inflammation biomarker levels, did not lead to any significant New York Heart Association functional improvement (odds ratio, 1.40; 95% confidence interval, 0.67–2.93; P=0.365) or affect

the likelihood of death or hospital stay for heart failure (P=0.839). There is no doubt that colchicine can indeed suppress proinflammatory activation in patients with CHF, but this effect does not appear to lead to any discernible clinical benefits.

CONCLUSIONS

Colchicine is a substance with potent anti-inflammatory properties, having a unique mechanism of action that enables safe use in patients with CV disease. The large-scale COLCOT and LoDoCo2 trials also showed benefits of low-dose colchicine (0.5 mg every day) for the reduction in recurrent CV events in patients with CAD. Colchicine is easily administered, generally well tolerated, and inexpensive. Therefore, these findings could strengthen the evidence in favor of this old, yet recently re-purposed drug in CAD.

ARTICLE INFORMATION

Ethical statement

Not applicable.

Conflicts of interest

The author has no conflicts of interest to declare.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (No. 2021R1A4A3031875).

ORCID

Hun-Jun Park, https://orcid.org/0000-0001-8009-9546

REFERENCES

1. World Health Organization (WHO). Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016. Geneva: WHO; 2018.
2. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.
3. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers 2019;5:56.
4. Ruparelia N, Chai JT, Fisher EA, Choudhury RP. Inflammatory processes in cardiovascular disease: a route to targeted therapies. Nat Rev Cardiol 2017;14:133–44.
5. Chen GY, Nunez G. Sterile inflammation: sensing and reacting to damage. Nat Rev Immunol 2010;10:826–37.
6. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–31.
7. Rodriguez de la Serna A, Guindo Soldevila J, Marti Claramunt V, Bayes de Luna A. Colchicine for recurrent pericarditis. Lancet 1987;2:1517.
8. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237–41.
9. Martinez GJ, Celermajer DS, Patel S. The NLRP3 inflammasome and the emerging role of colchicine to inhibit atherosclerosis-associated inflammation. Atherosclerosis 2018;269:262–71.
10. Ghattas A, Griffiths HR, Devitt A, Lip GY, Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? J Am Coll Cardiol 2013;62:1541–51.
11. Swirski FK, Libby P, Aikawa E, Alcaide P, Luscinskas FW, Weissleder R, et al. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. J Clin Invest 2007;117:195–205.
12. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357–61.
13. de Winther MP, Kanters E, Kraal G, Hofker MH. Nuclear factor kappaB signaling in atherogenesis. Arterioscler Thromb Vasc Biol 2005;25:904–14.
14. Dorweiler B, Torzewski M, Dahm M, Kirkpatrick CJ, Lackner KJ, Vahl CF. Subendothelial infiltration of neutrophil granulocytes and liberation of matrix-destabilizing enzymes in an experimental model of human neo-intima. Thromb Haemost 2008;99:373–81.
15. Henriksen PA, Sallenave JM. Human neutrophil elastase: mediator and therapeutic target in atherosclerosis. Int J Biochem Cell Biol 2008;40:1095–100.
16. Mazor R, Shurtz-Swirski R, Farah R, Kristal B, Shapiro G, Dorlechter F, et al. Primed polymorphonuclear leukocytes constitute a possible link between inflammation and oxidative stress in hyperlipidemic patients. Atherosclerosis 2008;197:937–43.
17. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. Science 2015;349:316–

20.
18. Andreu JM, Timasheff SN. Tubulin bound to colchicine forms polymers different from microtubules. Proc Natl Acad Sci U S A 1982;79:6753–6.
19. Ben-Chetrit E, Levy M. Does the lack of the P-glycoprotein efflux pump in neutrophils explain the efficacy of colchicine in familial Mediterranean fever and other inflammatory diseases? Med Hypotheses 1998;51:377–80.
20. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96:994–1002.
21. Paschke S, Weidner AF, Paust T, Marti O, Beil M, Ben-Chetrit E. Technical advance: inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. J Leukoc Biol 2013;94:1091–6.
22. Leung YY, Yao Hui LL, Kraus VB. Colchicine: update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 2015;45:341–50.
23. Abu-Fanne R, Stepanova V, Litvinov RI, Abdeen S, Bdeir K, Higazi M, et al. Neutrophil α-defensins promote thrombosis in vivo by altering fibrin formation, structure, and stability. Blood 2019;133:481–93.
24. Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol 2009;27:229–65.
25. Martinez GJ, Robertson S, Barraclough J, Xia Q, Mallat Z, Bursill C, et al. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. J Am Heart Assoc 2015;4:e002128.
26. Robertson S, Martinez GJ, Payet CA, Barraclough JY, Celermajer DS, Bursill C, et al. Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP3 inflammasome monocyte activation. Clin Sci (Lond) 2016;130:1237–46.
27. Vaidya K, Arnott C, Martinez GJ, Ng B, McCormack S, Sullivan DR, et al. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: a CT coronary angiography study. JACC Cardiovasc Imaging 2018;11(2 Pt 2):305–16.
28. Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol 2012;39:1458–64.
29. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, et al. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. Heart 2016;102:590–6.
30. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. Am J Cardiol 2007;99:805–7.
31. 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.
32. Nidorf SM, Fiolet AT, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383:1838–47.
33. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381:2497–505.
34. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS Randomized Clinical Trial. Circulation 2020;142:1890–900.
35. Bouabdallaoui N, Tardif JC, Waters DD, Pinto FJ, Maggioni AP, Diaz R, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020;41:4092–9.
36. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation 2015;132:1395–403.
37. Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, et al. Effect of colchicine on myocardial injury in acute myocardial infarction. Circulation 2021;144:859–69.
38. Abbate A, Kontos MC, Grizzard JD, Biondi-Zoccai GG, Van Tassell BW, Robati R, et al. 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.
39. Abbate A, Van Tassell BW, Biondi-Zoccai G, Kontos MC, Grizzard JD, Spillman DW, 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.
40. Deftereos S, Giannopoulos G, Panagopoulou V, Bouras G, Raisakis K, Kossyvakis C, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail 2014;2:131–7.