

CARDIOVASCULAR MEDICINE AND SOCIETY

Inflammation, Colchicine, and Atherosclerotic Disease



Is Familial Mediterranean Fever an Exception That Proves the Rule?

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In a recent large-scale epidemiologic report, 19 inflammatory disorders, including rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, psoriasis, lupus, Sjogren's syndrome, primary biliary cirrhosis, and inflammatory bowel disease, were all found to associate with significantly increased cardiovascular risk; this evidence is consistent with our current understanding that atherosclerosis is a disorder of systemic inflammation as well as hyperlipidemia.¹

Conspicuously absent from this list, however, was familial Mediterranean fever (FMF), an inflammatory disorder endemic to the Middle East. Yet, in contrast to almost all other inflammatory disorders, FMF is typically treated with long-term colchicine, an agent now approved by the U.S. Food and Drug Administration (FDA) as the first targeted anti-inflammatory indicated to reduce myocardial infarction, stroke, coronary revascularization, and cardiovascular death. This indication—virtually identical in its wording to that given by the FDA for statins—is the result of 2 randomized clinical trials which together have shown a 33% reduction in major adverse cardiovascular events among high-risk individuals randomly allocated to colchicine (0.5 mg orally once daily) compared with placebo.²

Is it thus possible that untreated FMF patients are at increased risk for atherosclerotic events but that their life-long treatment with colchicine has neutralized that risk? If so, what lessons can be gleaned from FMF regarding safety and efficacy that may be relevant for colchicine use in the general atherosclerosis population?

FMF is a prototypic autosomal recessive auto-inflammatory disorder common among Sephardic and North African Jews with additional high prevalence in Armenia, Turkey, Greece, and among Arab and Druze populations.³ Caused by mutations in the *MEFV* gene that encodes for a pyrin protein resulting in overexpression of interleukin-1 β , FMF is characterized by recurrent attacks of fever and serositis (peritonitis, pleuritis, synovitis, and pericarditis), lasting an average of 24 to 72 hours, and resolving spontaneously. Laboratory evidence during acute attacks indicates a systemic inflammatory process with leukocytosis and elevated erythrocyte sedimentation rate, C-reactive protein, fibrinogen, and serum amyloid A with an enhanced subclinical inflammatory state between attacks. Colchicine, the treatment of choice for FMF since 1972, reduces recurrent attack rates as well as their severity and duration and is additionally effective in preventing amyloidosis.

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Evidence addressing atherosclerotic risk in patients with FMF is limited, is controversial, and appears to depend in large part on documentation of colchicine adherence. In 2 retrospective studies with documented high rates of colchicine compliance, no increase in atherosclerotic risk has been reported.^{4,5} Specifically, in a study from a high-quality academic center with aggressive colchicine adherence and compliance, the prevalence of ischemic heart disease in 290 treated FMF patients was not significantly different when compared with prevalence among their spouses (a control group selected to address socioeconomic confounding) nor to a matched general population cohort without FMF.⁴ Similarly, in a small study of 23 well-characterized FMF patients admitted to a single academic medical center where colchicine compliance was very high, no evidence of increased atherosclerosis prevalence was observed.⁵

By contrast, in settings where colchicine compliance is uncertain, there appears to be evidence of elevated atherosclerotic risk among individuals with FMF. This is best seen in a large cross-sectional chronic disease registry study of 7,670 Israeli patients diagnosed with FMF (who received at least a single dose of colchicine) and an equal number of control subjects, largely taken care of in outpatient non-specialty settings.⁶ Here, a 33% increase in the prevalence of ischemic heart disease was observed, consistent with the hypothesis that chronic inflammation in the setting of FMF increases vascular risk. However, this general population registry analysis did not include data on colchicine adherence nor compliance, a significant issue because contemporary observational studies of FMF outpatients in the same geographic area indicate rates of nonuse or noncompliance for colchicine of at least 35% to 40%.

Finally, the hypothesis that untreated or inadequately treated FMF patients may be at elevated atherosclerotic risk is indirectly supported by genetic studies in which a proportional excess of *MEFV* variants has been reported among individuals with acute ischemia or prevalent coronary disease, including among individuals without FMF.⁷ Further, like colchicine, canakinumab—a monoclonal antibody targeting interleukin-1 β that is effective in FMF—has also proven to significantly reduce cardiovascular event rates.^{8,9}

In retrospect, it is likely that confounding by colchicine compliance explains conflicting results of studies investigating surrogate markers of atherosclerosis in FMF such as carotid intima-media thickness, impaired coronary microvascular function, or blood vessel elasticity. Improving colchicine compliance and encouraging clinicians worldwide to

institute common colchicine protocols for individuals with FMF will further reduce such variability.¹⁰

Taken together, we believe the available data are consistent with the hypothesis that chronic inflammation in untreated FMF is associated with elevated cardiovascular risk, but that this excess risk is substantially lower among highly compliant colchicine-treated patients. How, then, might data in the setting of FMF be informative to physicians just now considering the use of colchicine for the secondary prevention of myocardial infarction, stroke, and cardiovascular death? Two immediate issues are worth consideration.

First, long-term treatment with colchicine among patients with FMF is safe and shows no increase in risk for cancer, serious infections, or cause-specific mortality. This considerable safety data, consistent with the placebo-controlled atherosclerosis trials, should provide strong reassurance to the general medicine and cardiology communities as the daily colchicine dose given for FMF (1 to 2 mg orally daily) is substantially higher than the 0.5 mg oral daily dose approved for long-term use in atherosclerosis patients. Further, the 0.5 mg colchicine dose recommended for use in atherosclerosis does not adversely affect renal function or coagulation and has proven safe when used concomitantly with statins. Nonetheless, in keeping with established international guidelines related to the use of colchicine in FMF, we believe low-dose colchicine should not be given to individuals with significant renal or hepatic dysfunction and should be temporarily held when there is concomitant use of CYP-3A4 inhibitors or P-glycoprotein inhibitors such as clarithromycin, ketoconazole, fluconazole, and ritonavir.¹¹ We note that of the 2 major cardiovascular outcome trials of colchicine, one reported a small increase in risk of pneumonia whereas the other did not. We further acknowledge that additional colchicine trials in settings where placebo can ethically be used, such as in high-risk primary prevention, are warranted.

Second, despite 2 successful placebo-controlled trials, formal FDA approval, and guideline recommendations from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology, clinical uptake of low-dose colchicine for atherosclerosis treatment and prevention has been minimal. This lack of uptake reflects, in part, a paucity of marketing, promotion, and physician education programs regarding colchicine and atherosclerotic disease.

In this respect, the broad use of continuous lifelong colchicine in the setting of FMF provides us with

optimism that uptake of colchicine for the secondary prevention of vascular disease will increase over time. After all, despite a similar absence of promotion and advertising, physicians taking care of FMF patients routinely prescribe colchicine for a simple reason: their patients' lives depend on it.

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Dr Ben-Chetrit has received lecture fees from Sobi and Novartis (anti-IL-1 inhibitors in autoinflammatory diseases). Dr Falk has served as a consultant to Alnylam Pharmaceuticals and Alexion; and serves on data monitoring committees for Novo Nordisk and Alexion. Dr Ridker has received institutional research grant support from the National Heart, Lung, and Blood Institute, Novartis, and Novo Nordisk (to evaluate the role of anti-inflammatory agents including methotrexate, interleukin-1 inhibitors, and interleukin-6 inhibitors) as well as Kowa, Amarin, Pfizer, and Esperion; has served as a consultant to Novartis, Novo Nordisk, Janssen, Flame, Agepha,

Ardelyx, Zomagen, Horizon Therapeutics, CSL Behring, and Cardio Therapeutics (entities developing anti-inflammatory therapies including as examples colchicine, interleukin-1 inhibitors, interleukin-6 inhibitors, and agents that potentially target or interact with the NLRP3 inflammasome); has served as a consultant to AstraZeneca, Civi Biopharm, GlaxoSmithKline, SOCAR, Health Outlook, Montai Health, Eli Lilly, New Amsterdam, Boehringer Ingelheim, RTI, and Cytokinetics; has minority shareholder equity positions in Uppton, Bitterroot Bio, and Angiowave; and receives compensation for service on the Peter Munk Advisory Board (University of Toronto), the Leducq Foundation, Paris FR, and the Baim Institute. Dr Nidorf has reported that he has no relationships relevant to the contents of this paper to disclose.

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