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Is There a Role for Colchicine in Acute Coronary Syndromes?

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In this issue of the *Journal of the American Heart Association (JAHA)*, Martinez et al[1] demonstrate for the first time in man, that the crystal-induced NLRP3 inflammasome is activated within clinically stable coronary atherosclerotic plaque as evidenced by increased levels of IL-1ß and IL-18 in coronary sinus sampling, and that its expression is enhanced in the presence of unstable coronary plaque. In addition, they demonstrate that a low dose of colchicine could markedly reduce expression of these inflammatory markers within hours of ingestion. Although no specific mention was made of the tolerability of therapy it is unlikely that any untoward effects would have occurred with one exposure to the therapy.

These findings are important for two reasons. First, they are consistent with the thesis that local activation of cholesterol crystal-induced inflammation within atherosclerotic plaque may play a role in the progression and instability of atherosclerosis.[2–4] Second, the results are in keeping with suggestions that it may be possible to modify the natural history of patients with atherosclerosis by blocking activation of the NLRP3 inflammasome employing a low dose of colchicine.[5]

The challenge now is to determine whether these observations can translate into improved patient outcomes in routine clinical practice. Specifically, to determine whether there is a need to consider administering yet another therapy to what is already a complex therapeutic pharmacologic regime in patients presenting with acute coronary syndromes, and if so, to determine when such therapy should be initiated and how long it should be continued.

The need for additional therapy in patients with acute coronary syndrome is most clearly demonstrated by the results of the PROSPECT Trial, which examined the natural history of 697 patients' hospital with an acute coronary syndrome who underwent successful uncomplicated PTCA.[6] After 3 years of follow up, the cumulative risk of MACE (cardiac death, myocardial infarction, or hospitalization due to unstable or progressive angina) was <1% at 30 days, 15% at 12 months, and 20.4% at 3 years. Overall, 95% of clinical events occurred after the first month. In the first year almost half of the events related to progression of non-culprit lesions (NCL) but beyond that time clinical events were twice as likely to relate to progression of an NCL.

Hence, even in the contemporary setting, patients hospitalized with acute coronary syndromes remain at particularly high risk of MACE for at least 12 months due to progression of disease within and beyond the region of the culprit lesion despite intensive medical therapy with statins and dual antiplatelet therapy. These observations strengthen the rationale to consider the use of therapies such as colchicine that have the potential to dampen the inflammatory milieu that may lead to plaque instability and athero-thrombosis within native atherosclerotic plaque and the stent bed.[7]

The PROSPECT Trial also demonstrated that NCL, despite their mild appearance at angiography, were more likely to progress if they had a large plaque burden and a thin fibrous cap when assessed by intra-vascular ultrasound. Recent advances in imaging demonstrates that these lipid-rich vulnerable plaques often contain high concentrations of cholesterol crystals,[8,9] which is relevant given their potential to activate the NLRP3 inflammasome and the ability of colchicine to prevent and dampen crystal-induced inflammation.[10]

The observation that the vast majority of clinical events in the PROSPECT Trial occurred well beyond the first month of admission suggest that there may be no urgency in initiating colchicine therapy upon hospitalization unless it can be demonstrated to either reduce infarct size or reduce the risk of early stent stenosis, and to date there is only sparse data to suggest that colchicine has an effect on either outcome.

In the only animal study to examine the effect of colchicine on infarct size, pre-treatment with intra-venous therapy

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reduced the degree of neutrophil accumulation within myocardium but had no effect on infarct size.[11] In contrast, perioperative oral colchicine did reduce the levels of Troponin and CK-MB in patients undergoing coronary artery bypass surgery,[12] however, it is uncertain whether this effect might be seen or translate into limitation of infarct size in patients with acute coronary syndromes.

Colchicine has been demonstrated to have no effect on angiographic restenosis in patients undergoing simple balloon angioplasty[13] but has been shown to reduce the risk of neointimal hyperplasia in diabetic patients undergoing coronary stenting.[14] If this latter effect can be confirmed it would strengthen the rationale to evaluate early administration of colchicine in patients presenting with acute coronary syndromes, as many of these patients require coronary stenting during the index hospitalization. An adequately powered, randomized trial in this population is therefore needed.

There is an important rationale to continue to explore the benefit of anti-inflammatory therapy in patients with unstable coronary syndromes. Given the ability of a "single shot" of colchicine to effectively suppress activation of the NLRP3 inflammasome in these patients, it is tempting to examine this low-risk strategy in larger clinical trials, however, such studies should be extended to examine the effect of continuous therapy well beyond hospital stay, with the rationale of improving long-term recurrent atherothrombotic events.

The potential benefit of long-term colchicine in patients with stable coronary disease was suggested in retrospective studies in patients with FMF[15] and gout,[16] and was demonstrated prospectively in the LoDoCo trial in which the same (low) dose of colchcine used for secondary prevention in gout was safely and effectively employed in patients already taking high-dose statins and anti-platelet therapy.[17] A recent meta-analysis of colchicine trials has also been done, which points towards an overall benefit on cardiovascular risk reduction, in addition to its ability to reduce pericarditis.[18]

A number of going trials are exploring the potential of colchicine and other anti-inflammatory therapies including canakinumab and methotrexate for secondary prevention in patients with atherosclerosis.[19,20] Although early gastrointestinal intolerance will prevent the long-term use of low-dose of colchicine in up to 8% of patients, its low cost, ease of oral administration, widespread availability, proven long-term safety and efficacy for secondary prevention in the large majority of patients with recurrent gout, and FMF make it an attractive agent to continue to evaluate more fully in patients with atherosclerosis in the hope that it can fulfill an unmet therapeutic need in patients who, despite current therapies, remain at risk from their disease throughout their lifetime. The next decade will help define the role of inflammation as a target of cardiovascular risk reduction, and may usher in an entire novel mechanism of secondary prevention.[21]

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