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 (J>AHA), Martinez et al.1 demonstrate for the first time in man, that the crystal-induced NLRP3 inflamma-
some is activated within clinically stable coronary atheroscle-
rotic 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 atheroscle-
rotic plaque may play a role in the progression and instabili-
ity 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 observ-
vations 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 hospi-
talized 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 anti-
platelet 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. In contrast, periprocedural oral colchicine did reduce the levels of Troponin and CK-MB in patients undergoing coronary artery bypass surgery, 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 but has been shown to reduce the risk of neointimal hyperplasia in diabetic patients undergoing coronary stenting. 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 and gout, and was demonstrated prospectively in the LoDoCo trial in which the same dose of colchicine used for secondary prevention in gout was safely and effectively employed in patients already taking high-dose statins and anti-platelet therapy. 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.

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. 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.

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