Colchicine in Acute Myocardial Infarction: “Teaching New Tricks to an Old Dog”

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Editorial

Drug development is often not as linear as one would think. Repurposing of drugs for new uses is now common [1]. This is certainly the case of colchicine. Colchicine is one of the oldest anti-inflammatory drugs [2]. Colchicine was historically used as an unapproved drug to treat Mediterranean fever. In 2009, following compelling evidence in vitro and in vitro of the ability of colchicine to inhibit the assembly and activation of the NACHT-LRRPYD-containing protein 3 (NALP3 or NLRP3 [Nod-like receptor 3]) inflammasome in response to monosodium urate crystals, the United States Food and Drug Administration approved Colcrys™ for the treatment of Mediterranean fever and acute gouty arthritis [3].

The novel understanding of the mechanism of action of colchicine has opened the way to new investigation in the field of rheumatology and cardiology. Colchicine is now considered standard of care for the treatment of acute idiopathic or viral pericarditis [4]. More recently, colchicine has been studied in acute myocardial infarction (AMI) and heart failure. The NALP3/NLRP3 inflammasome is the major source of Interleukin-1β (IL-1β) in atherosclerosis and acute myocardial infarction [5,6]. IL-1β mediates progression of atherosclerosis, adverse cardiac remodeling after AMI, and worsening heart failure (HF) [6]. Considering the inhibitory effects of colchicine on the NALP3/NLRP3 inflammasome it was conceived that colchicine would prevent or improve cardiovascular disease. In the Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease [7], colchicine 0.5 mg daily for 3 years significantly reduced cardiovascular events in patients with stable coronary artery disease (5.3% vs. 16.0%, P<0.001, Table 1).

In an elegant study [8], patients with acute coronary syndrome showed enhanced myocardial production of IL-1β, consistent with active inflammation within the myocardium [9,10] and colchicine 1.5 mg given 6-24 hours prior to cardiac catheterization significantly reduced the myocardial production of IL-1β and the myocardial and systemic levels of Interleukin-6 (IL-6) (Table 1).

Consistent with a central role of the NALP3/NLRP3 in the inflammatory injury during ischemia-reperfusion [11,12], colchicine 1.5 mg followed by 0.5 mg 1 hour later and 0.5 mg twice daily for 5 days significantly reduced the size of the myocardial infarction in patients with ST-elevation AMI undergoing primary percutaneous coronary intervention [13] (Figures 1 and 2).

The exciting results of the pilot studies with colchicine require validation in appropriately powered clinical trials. The pilot studies are however informative on the tolerability of colchicine in patients with AMI or at risk for it. The gastrointestinal side effects appear to be the limiting factor, which however are dose dependent (ranging from 5% in the low dose study in stable patients [7] to 26% in the higher dose study in patients with AMI [13]). Therefore, it remains to be determined the optimal dose and duration of colchicine therapy, and whether other inflammasome inhibitors or IL-1β blocker would provide similar or better results [5,6].

<table>
<thead>
<tr>
<th>Year</th>
<th>Colchicine regimen</th>
<th>Comparison</th>
<th>Indication</th>
<th>Patients</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nidorf et al 2013</td>
<td>0.5 mg/day</td>
<td>Placebo</td>
<td>Established CAD, presenting for routine follow-up</td>
<td>n=532 (Active=282)</td>
<td>Treatment arm had significant reduction in ACS, out-of-hospital cardiac arrest, or ischemic stroke.</td>
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<tr>
<td>Martinez et al 2015</td>
<td>1 mg colchicine followed by 0.5mg 1 hour later, given 6-24 hours pre-catheterization</td>
<td>No colchicine</td>
<td>ACS or stable CAD, pre-cath</td>
<td>n=83</td>
<td>Treatment arm had significant reduction in transcoronary gradients of IL-1β, IL-18, and IL-6.</td>
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<tr>
<td>Deftereos et al 2015</td>
<td>2 mg loading dose followed by 0.5 mg twice daily, for a 5-day regimen</td>
<td>Placebo</td>
<td>STEMI &lt;12hrs from pain onset</td>
<td>n=151 (Active=77)</td>
<td>Treatment arm had significant reduction in infarct size measured as area-under-the-curve of CK-MB and of MRI-detemined infarct size.</td>
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Table 1: Colchicine in atherosclerosis and acute myocardial infarction.

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The story of colchicine should serve us as a reminder that Translational Medicine can be bidirectional: not only from bench-to-bedside but also bedside-to-bench. The clinical observation of the power anti-inflammatory effects of colchicine has driven further research leading to the discovery of the NALP3/NLRP3 inflammasome inhibitory activity in vitro which in turn lead to new clinical trials.

References

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