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Role of Lipid-Lowering Treatment in the Monocyte Phenotype and Chemokine Receptor Levels after Acute Myocardial Infarction

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Abstract : Introduction: Atherosclerosis is a progressive disease, characterized by lipid and fibrotic element deposition in large-caliber arteries. Conditions related to the development of atherosclerosis, as dyslipidemia, hypertension, diabetes, and smoking are associated with endothelial dysfunction. There is a frequent recurrence of cardiovascular outcomes after acute myocardial infarction and, at this sense, cycles of mobilization of monocyte subtypes (classical, intermediate and nonclassical) secondary to myocardial infarction may determine the colonization of atherosclerotic plaques in different stages of the development, contributing to early recurrence of ischemic events. The recruitment of different monocyte subsets during inflammatory process requires the expression of chemokine receptors CCR2, CCR5, and CX3CR1, to promote the migration of monocytes to the inflammatory site. The aim of this study was to evaluate the effect of lipid-lowering treatment by six months in the monocyte phenotype and chemokine receptor levels of patients after Acute Myocardial Infarction (AMI). Methods: This is a PROBE (prospective, randomized, open-label trial with blinded endpoints) study (ClinicalTrials.gov Identifier: NCT02428374). Adult patients (n=147) of both genders, ageing 18-75 years, were randomized in a 2x2 factorial design for treatment with rosuvastatin 20 mg/day or simvastatin 40 mg/day plus ezetimibe 10 mg/day as well as ticagrelor 90 mg 2x/day and clopidogrel 75 mg, in addition to conventional AMI therapy. Blood samples were collected at baseline, after one month and six months of treatment. Monocyte subtypes (classical - inflammatory, intermediate - phagocytic and nonclassical – anti-inflammatory) were identified, quantified and characterized by flow cytometry, as well as the expressions of the chemokine receptors (CCR2, CCR5 and CX3CR1) were also evaluated in the mononuclear cells. Results: After six months of treatment, there was an increase in the percentage of classical monocytes and reduction in the nonclassical monocytes ($p=0.038$ and $p < 0.0001$ Friedman Test), without differences for intermediate monocytes. Besides, classical monocytes had higher expressions of CCR5 and CX3CR1 after treatment, without differences related to CCR2 ($p < 0.0001$ for CCR5 and CX3CR1; $p=0.175$ for CCR2). Intermediate monocytes had higher expressions of CCR5 and CX3CR1 and lower expression of CCR2 ($p = 0.003$; $p < 0.0001$ and $p = 0.011$, respectively). Nonclassical monocytes had lower expressions of CCR2 and CCR5, without differences for CX3CR1 ($p < 0.0001$; $p = 0.009$ and $p = 0.138$, respectively). There were no differences after the comparison between the four treatment arms. Conclusion: The data suggest a time-dependent modulation of classical and nonclassical monocytes and chemokine receptor levels. The higher percentage of classical monocytes (inflammatory cells) suggest a residual inflammatory risk, even under preconized treatments to AMI. Indeed, these changes do not seem to be affected by choice of the lipid-lowering strategy.

Keywords : acute myocardial infarction, chemokine receptors, lipid-lowering treatment, monocyte subtypes
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