Early Intervention With Atorvastatin Modulates Th1/Th2 Imbalance in Patients With Acute Coronary Syndrome: From Bedside to Bench

To the Editor:

We read with great interest the recent article by Kinlay et al.1 In that article, they emphasized the antiinflammatory effect of high-dose atorvastatin in subjects enrolled in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, as reflected by lower levels of C-reactive protein (CRP) at 16 weeks. Recent studies showed that helper-T (Th) lymphocytes, which play an important role in the pathogenesis of acute coronary syndrome (ACS), can be divided into Th1 and Th2 cells on the basis of their cytokine profile. Indeed, we recently reported that a Th1 bias in Th1/Th2 immune response may play an important role in ACS patients as measured by the levels of Th1 and Th2 cytokines, such as interleukin (IL)-10, IL-12, and IL-18.2 Moreover, recent basic studies, so-called “bench” findings, demonstrated that statins exhibit potent immunomodulation of the regulation of Th1/Th2 polarization in animal or in vitro models.3,4 However, in the clinical setting, the immunomodulating effects of statins of Th1/Th2 polarization in patients with ACS have not been sufficiently determined.

We prospectively studied 19 male patients with Braunwald’s class III unstable angina (UA) and 21 age-matched male patients with stable angina (SA). The UA patients were randomly assigned to receive treatment with atorvastatin (10 or 20 mg/d) (group A, n = 10) or conventional therapy (group C, n = 10) within 12 hours after hospital admission. The group C patients with total cholesterol levels ≥ 220 mg/dL at 4 weeks after randomization were given colchicine 1.5g bid. Th-cell subsets were analyzed by 3-color flow cytometry after a 4-hour incubation with 25 ng/mL phorbol 12-myristate 13-acetate and 1 g/mL ionomycin in the presence of 10 μg/mL Brefeldin A, as described previously.5 Cytoplasmic cytokines were stained with antibodies against interferon (IFN)-γ and IL-4.6

Th1/Th2 ratio, estimated by the ratio of CD4+IFN-γ IL4+cells/CD4+IFN-γ IL4+ cells, was significantly higher in the UA group than in the SA group (14.0 ± 7.4 versus 6.1 ± 2.1, P < 0.0001). After 16 weeks, the total cholesterol levels were not different (A, 177 ± 26 mg/dL; C, 192 ± 32 mg/dL, P = 0.2). Nevertheless, the Th1/Th2 ratio significantly decreased in group A relative to group C (A, 14.0 ± 7.2 to 7.2 ± 2.3, P = 0.01; C, 14.0 ± 8.4 to 12.1 ± 4.5, P = 0.4; A versus C, P = 0.01). Moreover, CRP levels were positively correlated with Th1/Th2 ratio in group A (r = 0.66, P = 0.03).

These “bedside” findings firstly demonstrated that early intervention with low-dose atorvastatin also regulates Th1/Th2 imbalance, particularly, Th1 bias in ACS patients. Therefore, we believe that atorvastatin may exert a beneficial effect on ACS through its immunomodulatory property, as shown by the results reported by Kinlay et al.1

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Response

We thank Shimada et al for their report that examines further the antiinflammatory effects of statins in acute coronary syndromes. Whereas we found that the decline in C-reactive protein (CRP) in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study was accentuated by high-dose atorvastatin,7 they investigated the effects of atorvastatin on T-helper cell subsets (Th1 and Th2) as defined by the pattern of cytokines they express.

Their data show a higher ratio of Th1 to Th2 cells in plasma of patients with acute coronary syndromes compared with controls. This finding is consistent with a higher content of inflammatory cells in lesions responsible for acute coronary syndromes compared with stable angina,8 and the predominance of Th1 CD4+ cells compared with Th2 cells in atherosclerotic plaques.3 Th1 cells are considered pro-atherogenic because interferon-γ secreted by these cells decreases collagen production and activates macrophages—effects that favor plaque rupture.2,3

Furthermore, they found evidence for an antiinflammatory effect of high-dose atorvastatin reflected in a lower ratio of circulating Th1/Th2 cells. This observation supports our results with CRP in the larger MIRACL study, but also suggests that this therapy may reduce Th1 signaling mechanisms important in plaque instability.

The possibility that high-dose atorvastatin may selectively reduce Th1 cell activity by inhibiting CD40 ligation or other Th1-related mechanisms has some support in patients with hyperlipidemia or stable coronary syndromes,4,5 but requires further evaluation in the acute coronary syndrome setting.

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