T helper 1/T helper 2 balance and HMG-CoA reductase inhibitors in acute coronary syndrome: statins as immunomodulatory agents?

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This editorial refers to ‘Rapid immunomodulation by rosuvastatin in patients with acute coronary syndrome’ by A. Link et al., on page 2945

Immunity is derived from the Latin word immunitas, which means protection from civic duties and prosecution for a Roman Senator. Today, the principal function of the immune system is the protection of individuals against infectious agents and unsafe foreign (or endogenous) substances. This defence system comprises the early responses, namely innate immunity, and late reactions, called adaptive immunity. Innate immunity is the first line of defence that can be rapidly mobilized to detect pathogen-associated molecular patterns (PAMPs) using PAMP receptors (e.g. scavenger receptors and Toll-like receptors) on the surface of antigen-presenting cells (APCs), such as macrophages and dendritic cells. Adaptive immunity is the antigen-specific immune responses mainly consisting of lymphocytes. There are two types of adaptive immune responses: cell-mediated immunity and humoral immunity (Figure 1). In 1986, Mosmann et al. demonstrated for the first time that two types of CD4+ T helper (Th) cells, Th1 and Th2, can be distinguished based on their cytokine profile. The Th1 subset, which drives cell-mediated immunity, is heavily reliant on interferon (IFN)-γ and interleukin (IL)-12 in contrast to the dependence on IL-4 and IL-5 of the Th2 subset, which drives humoral immunity. The effector function of Th1 is the activation of macrophages, neutrophils, and CD8+ cytotoxic T lymphocytes to eliminate phagocytosed microbes and to remove injured tissues. In contrast, the effector function of Th2 is the stimulation of antibody production on B cells and plasma cells to neutralize microbes and their toxins. Multiple sclerosis, rheumatoid arthritis, type-1 diabetes, and graft-versus-host disease (GVHD), are considered as Th1-biased diseases. Allergic disease and systemic lupus erythematosus have been supposed to be Th2-predominant diseases, suggesting that overactivation of either pattern, namely Th1/Th2 imbalance, can cause a specific disease. Atherosclerosis, including acute coronary syndrome (ACS), is now clearly recognized to have a notable inflammatory reaction. Inflammatory cells, such as numerous CD4+ cells, accumulate in human atherosclerotic plaques. Recent clinical studies demonstrated that Th1-type cytokines dominate not only in atherosclerosis but also in ACS.2–4

The efficacy and safety of cholesterol treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are well established in all patients at risk of any type of major cardiovascular events. The impact of statin treatment in patients with wide spectrum of cholesterol levels has raised the question about the beneficial effects of statins beyond cholesterol lowering. Another mechanism by which statins can reduce future cardiovascular risk is recognized as being derived from lipid-independent effects, the so-called ‘pleiotropic effects,’ which are considered to modulate the generation of isoprenoids such as geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (farnesyl-PP). The binding of isoprenoids to the small GTP-binding protein Ras and Rho enables them to function in important intracellular signalling pathways. Statins have the potential to reduce isoprenylation of Ras and Rho which leads to broad signal transduction to regulate host homeostasis. Indeed, recent studies have revealed that the action of statins is much broader than we expected. Several clinical trials with statin treatment have been used in patients with autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis. The basis of hypothesis in these trials is derived from immunomodulatory effects of statins. Class II major histocompatibility complex (MHC) protein on the cell surface plays a crucial role in presenting antigens to T cells. Statins inhibit the induction of MHC class II protein and gene expression by IFN-γ stimulation through interference of MHC class II transcription activator.5

Link et al.6 have provided us with a new aspect of statins as immunomodulatory agents. Rosuvastatin treatment not only caused rapid decrease in plasma cytokine concentration, such as IFN-γ, IL-6, and tumour necrosis factor (TNF)-α, but also inhibited intracellular IFN-γ production in T lymphocytes in patients with ACS. Notably, these effects were observed even at 24 h after rosuvastatin
administration. In addition, rosuvastatin inhibited T cell immune response by suppressing Th1- and Th2-immune responses at 3 days after statin administration, and these effects lasted at least 6 weeks.

What is the mechanism? And how do we interpret these findings in the clinical setting? The present study by Link et al. confirmed the association between the pathophysiology of ACS and human immune system. Moreover, it clearly demonstrated that rosuvastatin is an immunomodulatory agent. It has been reported that the signal-transducer-and-activator-of-transcription (STAT) protein family, T-box expressed in T cells (T-bet), and GATA-binding protein 3 (GATA-3) regulate Th1 and Th2 cell differentiation (Figure 1). IL-12 and IL-4 made by Th2 cells drive antibodies production on B cells and plasma cells. Allergic disease, systemic lupus erythematosus, and abdominal aortic aneurysm have been supposed to be Th2-predominant diseases. Th1 and Th2 cytokines regulate each other’s function. Anti-inflammatory cytokine, IL-10, inhibits APC activation directly. Statin treatment promotes Th2 bias through the induction of STAT6 phosphorylation and inhibition of STAT4 phosphorylation. Moreover, statin inhibits the induction of MHC class II protein and gene expression through interference of HMG-CoA reductase inhibition.

A previous study also showed that early treatment with atorvastatin modulated Th1/Th2 balance in patients with ACS. However, it is not clear whether this rapid immune modulation for Th1/Th2 balance in patients with ACS is observed as a class effect. Although the authors of the present study mentioned that rosuvastatin rapidly inhibited a Th1-biased response independent of the plasma cholesterol levels, we need to focus on the existence of cholesterol in lipid rafts that are cell-membrane platforms in cholesterol-rich areas for clustering signal molecules. Since a recent report has suggested that inhibition of cholesterol synthesis by atorvastatin treatment altered the expression and distribution of lipid rafts on T cells, the difference in competence for HMG-CoA reductase inhibition may influence the differentiation and proliferation of T cells depending on how rapid and strong the clinical setting is, especially ACS as a highly activated immune response. Indeed, early administration of atorvastatin demonstrated excellent positive correlation between percentage change
in coronary plaque volume and percentage change in low density lipoprotein cholesterol levels in patients with ACS.\textsuperscript{11} The present study by Link et al.\textsuperscript{6} enrolled both non-ST-elevation and ST-elevation myocardial infarction as ACS. It is possible that Th1/Th2 imbalance may be involved with coronary artery inflammation or myocardial inflammation or both. It could be cleared if the authors analysed the data separately in two groups. Previous studies have already revealed a Th1 bias and modulation of Th1/Th2 imbalance by statin treatment in patients with unstable angina without troponin-I or -T elevation.\textsuperscript{4,9} However, further assessment is needed because myocardial damage might occur even in patients without myocardial necrosis.

Today, there is growing evidence that coronary heart disease, particularly ACS, is a Th1-biased immune disease and that statins as immunomodulatory agents ameliorate cardiovascular diseases. However, statin treatment can prevent only 30–40% of cardiovascular events. Moreover, we still do not know the entire pathophysiology of atherosclerosis even in terms of immunopathophysiology. It has recently been reported that development of abdominal aortic aneurysm, a part of atherosclerotic disease, correlated with skewed Th2 cytokine environments.\textsuperscript{12} Further detailed studies are also needed in this regard.

Conflict of interest: none declared.

References


Clinical vignette

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‘Edge-to-edge’ mitral valve repair: the ace of hearts

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A 32-year-old man underwent a successful surgical correction of a severe mitral regurgitation. The surgical procedure consisted of an 'edge-to-edge' repair of the valve, connecting the mid-portion of the anterior and posterior leaflets, associated with implantation of a mitral annuloplasty ring (Sovering Ø 38 mm; Sorin Biomedica Cardio). The 'edge-to-edge' or double orifice Alfieri technique represents an option in mitral valve repair when a severe mitral regurgitation. The surgical procedure consisted in the apical portion of the left ventricle depicting the shape of a playing card ace of hearts (Panel D).

Panel A. Parasternal short-axis view.

Panel B. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Panel C. "Edge-to-edge" mitral valve repair: the ace of hearts.

Panel D. Same apical four-chamber view as in Panel C.