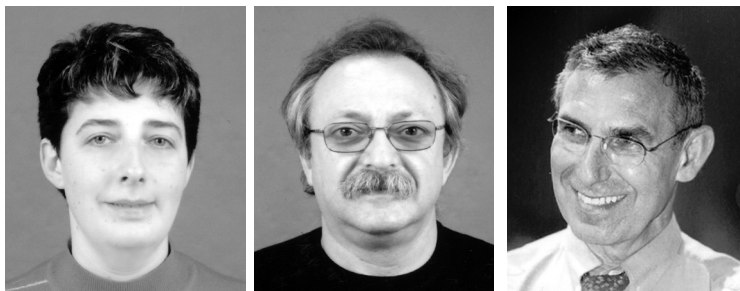# The Role of Inflammatory Cytokines in the Pathogenesis of Systemic Lupus Erythematosus-Related Atherosclerosis: A Novel Target for Treatment?

Atherosclerosis is a slowly progressive chronic inflammatory disease characterized by focal arterial lesions that can occlude the entire blood vessel and lead to sudden death. Lesions associated with cardiovascular events are those enriched in macrophages and other inflammatory cells. Activation of inflammatory cells within the lesions induces the release of substantial amounts of inflammatory factors and cytokines, which promotes more inflammation and associated tissue damage.

During the last few years it has become clear that several autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome, and systemic sclerosis are associated with higher rates of cardiovascular morbidity and mortality secondary to premature and accelerated atherosclerosis[1]. Thus, patients with SLE have a 5- to 6-fold increased risk for coronary vascular disease (CVD), and this excess risk is especially pronounced in younger women[2,3]. It has been also demonstrated that about 30% of patients with SLE have subclinical atherosclerosis[4].

Despite a large number of studies, the risk factors and proposed mechanisms of accelerated and premature atherosclerosis in SLE have continued to be the subject of investigations. First, atherosclerosis in SLE can be attributed to an increased frequency of traditional risk factors such as hypertension, dyslipidemia, obesity, and diabetes mellitus[3]. Additionally, it has been shown that atherosclerosis cannot be explained by Framingham risk factors alone[5] and may be associated with a combination of both traditional and nontraditional risk factors. Some novel or disease-related risk factors that may account for increased risk of atherosclerosis in SLE include inflammatory markers and cytokines: C-reactive protein (CRP), fibrinogen, and interleukin 6 (IL-6); immunological factors: antiphospholipid, anti-ß$_2$-glycoprotein I, antioxidized low-density lipoprotein, and anti-heat shock protein antibodies; abnormal coagulation factors: plasminogen activator inhibitor-1 and homocysteine; lipoprotein and modified lipids: lipoprotein(a) and high density lipoprotein (HDL).

The possibility that SLE itself may be atherogenic through chronic activation of the immune system and inflammation is of particular interest since both these mechanisms are involved in the pathogenesis of atherosclerosis. Considering the inflammatory nature of atherosclerosis, the question clearly arises: How is the accelerated arterial disease seen in SLE related to the interaction between different inflammatory and immune processes?

In this issue of *The Journal*, the interesting study of Asanuma and colleagues[6] on patients with SLE examines the association between the proatherogenic inflammatory cytokines IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) and risk factors for cardiovascular disease, as well as coronary artery calcifications. Plasma IL-6, MCP-1, and serum IL-8 were measured in 74 patients with SLE and in 85 healthy subjects. Coronary artery calcifications were determined by electron beam computed tomography. The investigations confirmed that levels of IL-6 and MCP-1 were higher in SLE patients than in controls and were linked with disease activity, as measured by the Systemic Lupus Erythematosus Disease Activity Index. Moreover, after adjusting for confounding covariates, including age, disease activity, Systemic Lupus International Collaborating Clinics Damage Index, smoking status, and systolic blood pressure, increased IL-6 levels were positively correlated with coronary calcifications and with Westergren erythrocyte sedimentation rate (ESR) and CRP. Of interest, elevated IL-6 levels found in patients with SLE were inversely correlated with HDL, whereas elevated

See Increased concentration of proatherogenic inflammatory cytokines in SLE, *page 539*

MCP-1 concentrations were linked with increased plasma triglycerides.

Several studies have provided data on the multifactorial role in atherogenesis of numerous proinflammatory cytokines, including promoting atherosclerosis-related inflammation, altering lipid metabolism[7], and contributing to plaque instability and rupture[8]. Asanuma, et al[6] highlighted numerous important points regarding the potential relationship in SLE between IL-6, MCP-1, and atherosclerosis.

IL-6, one of the most potent proinflammatory cytokines, induces acute phase protein production by hepatocytes. It is involved in the recruitment of inflammatory cells and lipid homeostasis and is associated with increased cardiovascular mortality and prognosis in the general population[9]. As noted above, IL-6 drives CRP production, which itself plays multiple roles, influencing key promoters of atherosclerosis; moreover, it appears as an independent predictor of coronary events[10]. In the study by Asanuma, et al[6] the strong correlation between IL-6 and acute phase reactants such as ESR and CRP raises the possibility that together these reflect the total inflammatory response associated with the disease. However, it has also been proven that the link between calcifications and elevated IL-6 levels remains significant after adjustment for ESR, and is borderline after adjustment for CRP. Since CRP production is driven by IL-6, an adjustment for CRP may camouflage the complete influence of IL-6 on atherogenesis; on the other hand the interaction between IL-6 and CRP in patients with SLE is controversial. Thus, several previous studies did not find a significant correlation between IL-6 and CRP levels in SLE patients in comparison to healthy subjects and patients with other rheumatic diseases[11]. Therefore, the relationship between IL-6 concentrations and the burden of atherosclerosis in SLE patients represents more than an epiphenomenon, and we agree with the authors that the measurement of IL-6 provides supplementary information in this cohort of SLE patients.

Patients with SLE have been described as having a lupus pattern of lipoproteins, including high levels of very low-density lipoprotein and triglycerides and low levels of HDL cholesterol, which represent a risk factor for CVD[12]. A number of mechanisms associated with the production of inflammatory cytokines may exacerbate atherogenic lipid profiles in SLE. Thus, IL-6 mediates inhibition of lipoprotein lipase (LPL)[7], as well as elevated circulating levels of anti-TNF-α, which are associated with high triglycerides and low HDL, contribute to the pattern of hyperlipidemia[13].

Identifying coronary artery calcifications is an established method for the detection of atherosclerosis, but as discussed above, proinflammatory cytokines could be involved early in atherogenesis, and their concentrations might play a special role before the development of a detectable plaque. Evaluation of the predictive value of the proinflammatory cytokines in SLE-related atherosclerosis will be a subject for further prospective investigations.

It may emerge that one of the important preventive measures to reduce cardiovascular complications in rheumatic diseases will be effective suppression of the underlying inflammatory rheumatic disease. This may have direct anti-inflammatory actions on atherosclerotic lesions, but may also suppress the disease activity and indirectly improve the profile of inflammation-related risk factors. For some drugs, such as corticosteroids, these potential benefits need to be set against possible untoward effects on the cardiovascular system. Thus, it has been recently reported that SLE patients with evidence of carotid atherosclerosis are less likely than those without evidence of atherosclerosis to have received prednisolone, cyclophosphamide, or hydroxychloroquine, suggesting that disease suppression may protect against atherosclerosis[14]. When treating patients with SLE, it is important to pay attention to a close monitoring of traditional risk factors, and guidelines for the treatment of hypercholesterolemia and hypertension should be reset in these patients.

Relatively little is known about the role of other treatments in SLE in relation to CVD. In this respect, the link between proinflammatory cytokines and atherosclerosis as well as some traditional risk factors allows additional opportunities for therapeutic interventions.

The reason for anticytokine therapy in SLE is based on the major role of cytokines in propagating the inflammatory processes responsible for tissue damage. Thus, IL-6 is instrumental in maintaining the autoinflammatory loop in SLE, and a rationale for IL-6 blockade has been recently demonstrated[15]. Notably, IL-6 has been shown to promote experimental lupus nephritis in rats that may be delayed by rat anti-IL-6 antibodies[16] or rat anti-IL-6 receptor antibodies[17]. Therefore, blockade of the IL-6 cascade may represent a novel target for prevention and therapy in SLE-associated atherosclerosis.

Inhibitors of tumor necrosis factor–α (TNF-α) have demonstrated efficacy in many inflammatory diseases including RA, ankylosing spondylitis, and Crohn's disease; but whether anti-TNF-α treatment also modulates atherosclerosis is still a mystery. The effect of this treatment on congestive heart failure (CHF) in RA patients is controversial and has been a subject of discussion[18]. By analogy with CHF, the importance of TNF-α blockade in SLE is also ambiguous, since TNF blockade may induce production of antibodies to double-stranded DNA and lupus-like disease in RA[19]. Nevertheless, the efficacy of anti–TNF–α in patients with SLE has been shown in an open-label study of infliximab in 6 patients with SLE[20]. In this trial, 3 patients with arthritis and 4 with nephritis (one with both clinical features) refractory to standard therapy were treated with infliximab, with a significant improvement in clinical manifestations. This observation suggests that uncoupling between autoantibody formation and inflammatory activity was found with TNF-α blockade, leading to a significant reduction of disease activity despite continuous production of anti-DNA autoantibodies[20].

Blockade of other inflammatory cytokines, which are directly involved in atherogenesis, may inhibit progression of atherosclerosis in SLE. For instance, the Th2 cytokine IL-4 may serve as a target for immunomodulation. Its potential involvement in atherogenesis has been implicated by the observation that fatty streak formation in IL-4 knockout mice immunized with HSP65 or *Mycobacterium tuberculosis* was significantly reduced when compared with lesions in wild-type controls[21].

Greater understanding of the mechanisms underlying accelerated atherosclerosis may not help to manage rheumatic disease but might provide some clues to the pathogenesis of atherosclerotic process in the general population. In the course of SLE, a variety of cytokines are dysregulated, several of which likely influence SLE-related atherosclerosis through propagating the immune and inflammatory response as well as altering lipid metabolism. Further studies are needed to understand more completely the mechanisms by which proinflammatory cytokines may influence the development of accelerated and premature atherosclerosis in SLE. Novel therapeutic approaches will be developed that target the causes of the inflammatory process in atherosclerotic plaques.

ORA SHOVMAN, MD,
Center for Autoimmune Diseases,
Department of Medicine B, Sheba Medical Center;
BORIS GILBURD, MD, PhD,
Sackler Faculty of Medicine,
Incumbent of the Laura Schwarz-Kipp Chair for Research of Autoimmune Diseases, Tel-Aviv University;
YEHUDA SHOENFELD, MD, FRCP(Hon),
Head, Center for Autoimmune Diseases,
Department of Medicine B, Sheba Medical Center;
and Sackler Faculty of Medicine, Tel-Aviv University

Address reprint requests to Dr. Shoenfeld; E-mail: shoenfel@post.tau.ac.il

REFERENCES

1. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112:3337-47.
2. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;14:408-15.
3. Doria A, Sherer Y, Meroni PL, et al. Inflammation and accelerated atherosclerosis: basic mechanisms. Rheum Dis Clin North Am 2005;31:355-62.
4. Bruce IN, Burns RJ, Gladman DD, et al. Single photon emission computed tomography dual isotope myocardial perfusion imaging in women with systemic lupus erythematosus. I. Prevalence and distribution of abnormalities. J Rheumatol 2000;27:2372-7.
5. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-7.
6. Asanuma Y, Chung CP, Oeser A, et al. Increased concentration of proatherogenic inflammatory cytokines in systemic lupus erythematosus: relationship to cardiovascular risk factors. J Rheumatol 2006;33:539-45.
7. Mol MJ, Demacker PN, Stalenhoef AF. The role of modification of lipoproteins and of the immune system in early atherogenesis. Neth J Med 1993;43:83-90.
8. Galis ZS, Muszynski M, Sukhova GK, et al. Enhanced expression of vascular matrix metalloproteinases induced in vitro by cytokines and in regions of human atherosclerotic lesions. Ann NY Acad Sci 1995;748:501-7.
9. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506-12.
10. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
11. Williams RC Jr, Harmon ME, Burlingame R, et al. Studies of serum C-reactive protein in systemic lupus erythematosus. J Rheumatol 2005;32:454-61.
12. Ilowite NT, Samuel P, Ginzler E, et al. Dyslipoproteinemia in pediatric systemic lupus erythematosus. Arthritis Rheum 1988;31:859-63.
13. Svenungsson E, Fei GZ, Jensen-Urstad K, et al. TNF-alpha: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. Lupus 2003;12:454-61.
14. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2399-406.
15. Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. Lupus 2004;13:339-43.
16. Finck BK, Chan B, Wofsy D. Interleukin 6 promotes murine lupus in NZB/NZW F1 mice. J Clin Invest 1994;94:585-91.
17. Mihara M, Takagi N, Takeda Y, Ohsugi Y. IL-6 receptor blockage inhibits the onset of autoimmune kidney disease in NZB/W F1 mice. Clin Exp Immunol 1998;112:397-402.
18. Sarzi-Puttini P, Atzeni F, Shoenfeld Y, et al. TNF-alpha, rheumatoid arthritis, and heart failure: a rheumatological dilemma. Autoimmun Rev 2005;4:153-61.
19. Charles PJ, Smeenk RJ, De Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 2000;43:2383-90.
20. Aringer M, Graninger WB, Steiner G, et al. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum 2004; 50:3161-9.
21. George J, Shoenfeld Y, Gilburd B, et al. Requisite role for interleukin-4 in the acceleration of fatty streaks induced by heat shock protein 65 or Mycobacterium tuberculosis. Circ Res 2000;86:1203-10.