EDITORIAL COMMENT

The Monocyte: The Key in the Lock to Reduce Stent Hyperplasia?*

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It has been more than 20 years since Essed and associates (1) first documented intimal proliferation after percutaneous transluminal coronary angioplasty (PTCA) as a cause of restenosis. During this interval, enormous progress has been made in defining the pathogenetic mechanism of human restenotic lesions. Today, there is a general consensus that restenosis involves the interactions of different cytokines, growth factors, vascular elements, blood cells, and extent of injury. Based on the experience derived from experimental models, cell culture, and human pathologic evidence, as well as angiographic, angioscopic, and intravascular ultrasonography observations, the sequence of events that take place in the artery after stent implantation and that characterize the restenotic process consists of thrombosis, recruitment of inflammatory cells, and proliferation/remodeling (2,3). A fundamental difference between restenosis occurring after balloon angioplasty and stenting is that in the latter the remodeling component is absent and the only component is hyperplasia as a part of the reparative process to trauma and as a reaction to the implant of metal (4). As a result of vessel wall injury, medial smooth muscle cells (SMCs) and adventitial myofibroblasts proliferate and migrate into the intimal layer, resulting in neointimal formation and lumen loss. Recent reports, however, suggest that SMC proliferation may not be the key event in lesion formation and that other cell types may play a more significant role (5). Moreover, stent-induced appearance of activated platelets, which promotes leukocyte (monocytes and granulocytes) recruitment to the injured vessel wall and leukocyte-platelet aggregates in blood, as well as elevated plasmatic levels of monocyte-related cytokine interleukin-6, has been observed to correlate with clinical outcome. In particular, activated monocytes may contribute to neointimal thickening (5) by generating reactive oxygen species through the production of growth and chemotactic factors (6), binding to a broad repertoire of ligands (7), or by matrix metalloprotease production capable of degrading matrix constituents and consequently facilitating cell migration (8).

In this issue of the Journal, Fukuda et al. (9) present the results of a study evaluating the relationship between monocytes and neointimal growth after coronary artery stenting. The authors divided the patient population into two groups: with and without in-stent restenosis. In addition, they evaluated a control group who underwent diagnostic angiography without coronary intervention. A total of 107 patients who underwent coronary artery stenting were studied. Circulating monocyte count was obtained for all patients daily for seven days. In addition, at six-month follow-up patients underwent angiographic and volumetric intravascular analysis. The results are in accordance with previous observations in animal models with stenting and with angioplasty alone. Despite the fact that no flowcytometric methods have been used to measure early and late circulating leukocyte activation status, this study clearly demonstrates that circulating monocytes increase after stent implantation and the peak monocyte count correlates to the in-stent neointimal volume. Thus, the authors concluded that circulating monocytes play a role in the process of in-stent neointimal hyperplasia.

Indeed, several experimental studies in different animal models suggest that intimal inflammation is a determinant of in-stent neointimal growth (10,11). In stented rabbit iliac arteries, Rogers et al. (12) demonstrated that monocyte adherence correlated with neointimal size (r = 0.96). A subsequent study from the same group demonstrated a peak monocyte adherence to the lumen surface three days after stenting, which correlated in turn with neointimal formation (r² = 0.916) (13). In porcine injury models, lymphohistiocytic cell infiltration around stent struts was associated with increased neointimal thickness and percent lumen area stenosis (14). Furthermore, a number of studies demonstrate that the blockade of inflammation and cell adhesion molecules important for neutrophil recruitment attenuates neointimal growth (15). M1/70, a CD11b-blocking monoclonal antibody, was shown to inhibit neutrophil infiltration and medial SMC proliferation in a balloon denudation model (16). The blockade of monocyte chemoattractant protein-1 (MCP-1) and integrins VLA-4 (CD49d/CD29), molecules responsible for monocyte/macrophage infiltration/activation, attenuated neointimal formation, and negative remodeling in different animal models (17–19). Recently, Manka et al. (20) reported in a carotid artery injury model that apolipoprotein E–deficient mice with targeted disruption of the P-selectin gene, a protein stored in the α-granules of platelets and Weibel-Palades bodies of endothelial cell bonding to circulating monocytes and leukocytes, exhibited dramatic decreases in monocyte infiltration into the arterial wall, associated with significant decreases in neointimal hyperplasia (20). Finally, administration of recombinant human interleukin-10

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Can the same evidence be translated into the clinical arena and related to increased neointimal formation in patients undergoing percutaneous interventions? Inflammatory cells associated with coronary stent placements in humans have been described by histomorphometric evaluation in autopsy series both early and long term after stent placement (22,23). Neutrophils surrounding stent strut usually are present in the early phase after implant, whereas macrophages and lymphocytes are seen both in the early and late phases (24). In addition, the inflammatory response seems to be related not only to the intensity of injury (25) but also to the underlying wall morphology: that is, stent struts in contact with necrotic core or damaged media are associated with more severe inflammatory cell infiltration than struts in contact with fibrous plaque. In addition, chemokines and proinflammatory cytokines that regulate migration and infiltration of leukocytes at the site of vascular injury, and subsequently cause leukocyte activation, have also been demonstrated in humans. In this setting, up-regulation of Mac-1, a leukocyte integrin (CD11b/CD18, $\alpha_\text{M} \beta_2$) that promotes adhesion and transmigration of leukocytes and monocytes, is associated with increased restenosis in patients subjected to percutaneous revascularization (26–28). Plasma levels of the MCP-1 are significantly increased one day after PTCA, and patients with restenosis had significantly higher MCP-1 levels after PTCA than those without restenosis (29). Similarly, Hoki-moto et al. (30) showed significantly higher MCP-1 values in samples collected 48 h and three months after PTCA in patients who developed restenosis. These data, along with the current study, support the view that inflammation plays a role in neointimal thickening and suggest the validity of targeting leukocyte recruitment for preventing clinical restenosis.

How can we counteract the adhesion and chemotaxis of inflammatory leukocytes after stenting when these events seem to be crucial for the development of restenosis? High doses of aspirin, the most widely used anti-inflammatory drug, have been shown to significantly inhibit leukocyte attack in a three-dimensional human coronary in vitro model (31) but not in the clinical arena (32,33). Red wine consumption has been shown to inhibit MCP-1 expression and reduce the intimal response to injury in animal models (34). Recently, the Immunosuppressive Therapy for the Prevention of Restenosis After Coronary Artery Stent Implantation (IMPRESS) study, in which patients with persistently high C-reactive protein values (>5 mg/dl) who underwent successful coronary artery implantation had a 54% decrease in in-stent late loss when treated with oral immunosuppressive prednisone therapy (35). Therefore, it has been hypothesized that the high systemic inflammatory response may be due to further activation of the inflammatory process within the plaque itself and to injury during coronary stenting. On the contrary, other studies examining the role of systemic corticosteroid administration failed to show any significant reduction after balloon angioplasty (36,37). However, in the majority of these studies, corticosteroids were used after balloon angioplasty rather than after stenting, and a single dose was frequently given (38,39). Most importantly, no attempt has been made to target both treatment and dosage to patients with high inflammatory biochemical and cellular markers. The conflicting results in the field of anti-inflammatory therapy for the prevention of in-stent hyperplasia may be due to the fact that the inflammatory component predominates only in some patients. In the present study of Fukuda, the correlation between the increase in monocyte count and post-stent hyperplasia had an $r$ value of 0.44, which explains only part of the problem. In an elegant study, Danenberg et al. (40) recently demonstrated that the systemic inactivation and depletion of monocytes and macrophages by liposomal clodronate in animal models reduced neointimal hyperplasia and restenosis. Along the lines of suppression of monocyte activation, a recently proposed approach using this concept will soon be investigated in humans. Nitrogen-containing bisphosphonates are inhibitors of the mevalonate pathway and, therefore, block prenylation of small GTPases, such as Ras, Rho, and Rac. These proteins regulate a variety of cell processes important for monocyte/macrophage function, including cell morphology, membrane ruffling, trafficking of endosomes, and cell survival (41). Once the liposome containing the bisphosphonate enters the monocyte/macrophage, the liposome undergoes lipolysis, the drug is released, and cell activity is halted. Cells that do not possess the ability to phagocytose are not affected, and a free drug will either be cleared without cellular absorption or transiently complexed to bone, decreasing systemic toxicity. In addition, bisphosphonate-loaded liposomes can engage monocyte/macrophage both locally and systemically, providing for biological homing of this strategy.

It is worthwhile to note that whatever strategy we may use, the possibility of either growth rebound of neointimal hyperplasia after therapy cessation or development of neutralizing antibodies, which may render the anti-inflammatory strategy ineffective over time, should be taken into account. The study by Fukuda and his colleagues (9) indicates that measurements of monocytes may be of assistance in identifying patients who are prone to restenosis after stenting. A combination of present and future strategies will probably represent the final therapeutic solution to the problem of neointimal hyperplasia. As Andre Cournard remarked in his Nobel lecture of December 11, 1956, “The cardiac catheter was . . . the key in the lock”; perhaps drug-eluting stents associated with anti-inflammatory strategies will become a “passe-partout” (master key) in the everyday struggle to reduce restenosis in interventional cardiology.
REFERENCES


