Clinical Feasibility of Molecular Imaging of Plaque Inflammation in Atherosclerosis

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Molecular imaging of various components of atherosclerotic plaques has been proposed, and proof of principle has been demonstrated in experimental models of disease (1). These preclinical studies have predominantly targeted plaque inflammation with the premise that the extent of inflammation would determine the vulnerability of the plaque to rupture. Plaque inflammation has been detected by targeting alterations in monocytes that facilitate their migration to the neointima, ensure efficient scavenging of insudated lipid, oversee their transformation to foam cells or mediate cell death (1).

Molecular targets have also included events that are associated with or consequent to inflammation, such as production of cytokines and metalloproteinases. Although these experimental molecular imaging studies have offered significant promise, translational data in the clinical setting has just started to emerge. Clinical studies of molecular targeting are the major focus of the following review.

We have referred to some of the early molecular imaging attempts that labeled white blood cells to follow their localization and labeled lipoproteins to trace their destination in the inflammatory cells in plaques (1). Even though the incorporation of radio-labeled components in the plaque may not have been adequate, these studies created a sound foundation for the development of imaging strategies of the future.

Pathologic Basis of Inflammation Imaging

Vulnerable plaques have typically large necrotic cores that are covered by thin fibrous caps (2). Many foam cells are seen around the necrotic cores. There is extensive inflammation within the fibrous caps; the more macrophages, the thinner the cap. Migration of monocytes to the subintimal layers of the plaque is associated with de-
development of receptors for chemoattractant factors, such as monocyte chemotactic protein-1 (MCP-1); adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) (1); and expression of scavenger receptors, including SRAI/II, CD68 and FcRlII.

In addition to upregulation of various surface receptors, foam cells in the neointima release numerous cytokines, such as interleukin-1, tumor necrosis factor-α and MCP-1 (3). Activated macrophages also release metalloproteinases and other proteolytic enzymes, such as cathepsins, which lead to degradation of the matrix, thinning of the fibrous cap and positive outward remodeling of the vessel wall. Cell death is commonly observed in the vulnerable plaque; macrophage death leads to expansion of the necrotic core and perpetuates plaque instability (4). More than 40 percent of macrophages at the site of fibrous cap rupture are also in the process of cell death by apoptosis. It has been reported that dying macrophages may produce tissue factor (5) and metalloproteinases.

Molecular Imaging of Plaque Inflammation

The characteristic alterations that evolve during monocyte infiltration to the neointima and lipoprotein ingestion vary based on different phases of plaque development and have been targeted successfully by radiolabeled autologous leukocytes (Fig. 1) (6), low-density lipoprotein (LDL) (7) and Fc fragments of immunoglobulin (8). More recent experimental studies have used radiolabeled ligands of cytokine and adhesion molecule receptors, including MCP-1 and VCAM-1, or cytokines released by infiltrating macrophages, such as metalloproteinase (1).

It is not entirely clear if such a characterization would be of clinical significance or which candidate molecule would be most informative. However, few recent correlative studies have demonstrated that the presence of activated or apoptotic macrophages are associated with culprit lesions underlying an acute coronary event. The macrophages with high respiratory burst have been clinically recognized by 18F-labeled FDG imaging (9), and dying macrophages by technetium-99m annexin-A5 (AA5) (Fig. 1) (4,10). Presence of active inflammation should predict plaque vulnerability if information is obtained before the occurrence of an acute event.

FDG Imaging of Plaque Instability

PET imaging studies for localization of malignant tumors have reported incidental 18F-FDG uptake in the carotid, coronary, iliac and femoral arteries, and thoracic and abdominal aorta in up to 50 percent of patients. In prospectively studied patients with ultrasonic evidence of carotid atherosclerosis, FDG uptake was seen in 30 percent of patients (11). Glucose uptake in atherosclerotic plaques has been hypothesized to represent inflammatory activity, and there is a direct correlation between carotid FDG uptake (expressed as the target-to-background ratio of standardized uptake value) and macrophage density (mean percentage staining of CD68-positive cells) in the carotid endarterectomy specimens (r = 0.85, P < 0.0001) (12). 18F-FDG uptake does not correlate with plaque area, thickness or smooth muscle cell density.

Serial prospective 18F-FDG PET studies have reported an excellent interobserver, intraobserver and interscan reproducibility (13). The effect of statin intervention on FDG uptake has been reported in patients with carotid atherosclerosis (14), wherein the follow-up PET scans revealed significant reduction in FDG accumulation after therapy. FDG uptake, however, does not resolve in response to only dietary modifications (14).

Although various case reports and retrospective studies (15) have demonstrated anecdotal 18F-FDG uptake in coronary arteries in oncologic patients, a recent prospective 18F-FDG PET study with multislice CT demonstrated the feasibility of precise 18F-FDG localization in coronary arteries (Fig. 2) (16). In this study, myocardial 18F-FDG uptake was almost entirely suppressed (by a high-fat diet and restriction of carbohydrate meals for one day before the study and administration of β-blockers on the day of the study) for better target recognition.

The study also took advantage of CT angiography and enrolled patients who had undergone coronary stent implantation for acute coronary syndrome or chronic stable angina; CT angiography and stent location allowed precise coregistration of FDG uptake at the plaque site. Culprit lesions in acute coronary events demonstrated significantly higher FDG uptake (Fig. 2) than did target lesions in chronic disease. Although it will be necessary to develop measures to contain radiation burden imposed by combined PET/CT studies, this study holds a promise of radical strategic shift in coronary artery disease management.

Annexin Imaging of Inflamed Plaques

Because apoptotic cells express phosphatidylserine on their cell surface and AA5 has a high affinity for binding to phosphatidylserine, imaging with 99mTc-labeled AA5 has been used to evaluate the feasibility of the detection of unstable plaques. AA5 has been extensively used for noninvasive imaging of experimental atherosclerotic lesions (4). There was a direct correlation of AA5 uptake with macrophage burden and the magnitude of histologically verified apoptosis.

It was subsequently indicated that pharmacologic intervention using stents and caspase inhibitors could reduce the extent of apoptosis in experimental atherosclerosis models (17,18). Studies of porcine atherosclerosis have demonstrated the feasibility of coronary imaging with radiolabeled AA5 (19). AA5 has also been used...
in a small pilot study for imaging of carotid atherosclerosis in patients with recent or remote cerebrovascular accidents (10). AA5 uptake was reported only after recent cerebrovascular accidents and not seen in patients being treated with statins.

AA5 binding was histologically localized to apoptotic macrophages and also to the red blood cell membranes embedded in necrotic cores. Radiolabeling of AA5 with PET-compatible radiotracers, such as $^{125}$I and $^{18}$F, is under way and may provide better avenues for coronary vascular imaging.

Conclusions

The likelihood that atherosclerotic plaques will result in acute vascular events is intimately associated with the morphologic traits of the plaque and the extent of inflammation. A noninvasive strategy designed to monitor the extent of plaque inflammation may allow identification of unstable plaques, and serial interrogation may determine the efficacy of intervention.

$^{18}$F-FDG uptake, which has been commonly used in oncologic practice, offers information about plaque inflammation and allows serial investigation. The feasibility of coronary imaging with $^{18}$F-FDG has evoked tremendous enthusiasm in the imaging community. Successful $^{18}$F-FDG imaging of coronary arteries has also encouraged investigation with other promising molecules, such as annexin. It is conceivable that the high-risk patients identified by clinical tools, including genetic information and biomarkers, will in the future be more accurately stratified by imaging targeted at morphologic and functional characterization of high-risk plaques.

References


Clinical Trials Workshop at SNM Annual Meeting

The content from the recent, sold-out workshop on the SNM Clinical Trials Network will be repeated in a one-day categorical at SNM’s 56th Annual Meeting in Toronto, June 13, 2009. There will also be a CE Session on Sunday devoted to manufacturing issues.

If you missed the February workshop, this is your chance to get acquainted with the SNM Clinical Trials Network and learn how you can provide imaging services to therapeutic multicenter clinical trials or take advantage of SNM’s multicenter IND for FLT imaging.