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Iron Oxide Magnetic Resonance Imaging for Atherosclerosis Therapeutic Evaluation:

Still "Rusty?"*

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Multicenter, randomized, placebo-controlled "outcome" trials with long-term follow-up of thousands of patients are currently being used to evaluate new therapies for cardiovascular disease. Owing to improvements in risk factor modifications as well as to the concomitant use of established treatments, such as statins, leading to a drop in clinical event rates, it is projected that the number of patients enrolled in trials may need to be increased to separate the effect of new therapies from those of established ones. Recently, the JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) study (1) showed the importance of serologic measures of inflammation. These new in-blood markers may, however, be insufficient when used alone as predictive models of mortality and morbidity (2). Several recent cardiovascular trials have opted to use imaging (quantitative coronary angiography, carotid intima media thickness with ultrasonography, coronary intravascular ultrasonography, and so forth) to measure the impact of promising novel therapeutics (3). Validation of these in vivo diagnostic imaging methods may allow for shorter follow-up times and eventually, for smaller patient populations tested.

Many imaging technologies focus primarily on changes in luminal size or vessel wall area. New imaging methods that focus on vessel wall composition, and relate to the underlying plaque pathogenesis, may provide useful information not readily available by standard morphometric measurements. For example, noninvasive magnetic resonance imaging (MRI) using ultrasmall superparamagnetic iron oxide (USPIO) particles has been shown to identify inflammatory changes by monitoring macrophage uptake, a major component of high-risk (vulnerable) plaques.

To date, there have been no published studies that show correlations between the dose of prescribed statin and in vivo changes in macrophage distribution. The study by Tang et al. (4) in this issue of the *Journal* is the first prospective molecular MRI study that tries to correlate the in vivo effects of statin therapy on carotid plaque inflammation, as observed by MRI (5). The study found a significant reduction from baseline in USPIO-enhanced MRI-defined plaque

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inflammation in the high-dose atorvastatin group at both 6 weeks and at 12 weeks after treatment. Such changes were not observed in the low-dose statin (i.e., atorvastatin 20 mg) group. These findings provide additional in vivo evidence that high-dose statin (i.e., 80 mg) therapy might have a beneficial effect on plaque "stability." Furthermore, these changes in USPIO-defined plaque inflammation could be observed within 6 weeks, a relatively short treatment interval compared to the prolonged periods (years) that are required to observe changes in plaque burden. This study may also indicate that reductions in plaque inflammation may play an important role in the mechanism underlying the early beneficial effects of statins.

If adequately validated, USPIO-enhanced MRI methodology may be a useful imaging biomarker for the screening and assessment of therapeutic response to "anti-inflammatory" interventions in patients with carotid atherosclerotic lesions. However, before USPIO-MR can be routinely used for multicenter clinical testing, several issues with regard to the current study need to be examined. The relatively small patient group tested limits generalization of the dose-response observed in this study. Although the authors exhibit a weak correlation of the MRI data to the microemboli count on transcranial Doppler, the study still does not correlate the MRI findings to any hard clinical end points.

Although the results of the ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) study (4) are exciting and show the potential of USPIO-MRI for longitudinal evaluation of plaque inflammation, the utility of the method is counterbalanced by a lack of quantitative rigor as compared with other current imaging modalities. For example, the reproducibility and the repeatability of vascular inflammation imaging using ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) is well validated and established (6). Studies using FDG-PET/CT have shown a reduction in inflammatory burden at 3 months after statin treatment (7-9). Limited data are available, however, for clinical studies using USPIO-MRI. As a result, aspects of USPIO-MRI quantification need to be addressed before using this method in large multicenter clinical trials. The authors rely on visual observation and changes in signal intensity to determine USPIO uptake. However, differences in patient positioning, coil inhomogeneities, noise, and other artifacts may all induce signal loss and may not be indicative of USPIO uptake. The conclusions obtained from this study would be greatly strengthened by the addition of validated semiquantitative analyses. Moreover, imaging improvements, such as the use of positive contrast or whitemarker data acquisition (gradient echo acquisition for superparamagnetic particles, inversion recovery on-resonance water suppression, ultra short echo time, and so forth), which may be acquired within the same imaging session, are expected to improve image interpretation and data analysis (10). Finally, the nature of the atherosclerotic plaque, as described on histology, is typically nonconcentric and may not benefit from a quadrants approach, as used in the ATHEROMA study.

MRI does not expose the patient to radiation, thereby allowing for long-term and serial monitoring. Unfortunately, the USPIO (Sinerem, Guerbert, Roissy, France) used in the ATHEROMA study is currently not approved by the Food and Drug Administration and is considered investigational. Sinerem was originally developed as a contrast agent for the lymphatics and bone marrow (11,12); as a result, high lymphatic uptake is expected. Because the signal loss observed by USPIO is caused by dephasing of diffusing water protons, blooming effects (or signal loss over a larger distance) may be observed. Owing to the proximity of the lymphatics to the arterial wall, the data obtained using the quadrant analysis approach may become biased and/or skewed by lymphatic tissue included in any given quadrant.

A potential clinical concern relates to the general use of iron oxide particles for imaging of atherosclerotic plaques. Studies have shown that macrophages metabolize iron oxides by degrading the iron core, with subsequent release of soluble iron (13). Although most of this

iron may be captured and stored as ferritin, there is a potential for the release of soluble iron (a known oxidant) into an inflammatory environment. As a result, the metabolism of iron may lead to the generation of superoxidases, which may further promote the oxidation of low-density lipoprotein cholesterol. Oxidized low-density lipoprotein cholesterol has been implicated in the pathogenesis of atherosclerosis and may lead to plaque destabilization (14). Therefore, studies should be performed to ensure that metabolism of the USPIO does not promote plaque destabilization if this technique is to become routinely used in clinical settings. Imaging of inflammatory changes using USPIO also requires 2 scans: a pre-contrast scan and a post-contrast infusion scan at each imaging time point.

Although the current statin trial using noninvasive carotid USPIO-MRI is interesting and unique, further studies are required to determine the clinical applicability of this methodology for use as an end point in clinical trials. The valuable ATHEROMA study presented by Tang et al. (4) adds further momentum to the importance of using diagnostic molecular imaging in the development of future cardiovascular therapies.

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