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CLINICAL TRIAL REPORT

The ATHEROMA Study: Rapid Anti-inflammatory Effects of High-Dose Statin Pharmacotherapy Illuminated by Molecular MRI

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Rating

• Of importance.

Introduction

Statins are thought to reduce inflammation in atherosclerotic plaques; however, to date, in vivo data in clinical subjects demonstrating this effect and statin-dose dependency are limited. Molecular MRI of carotid plaque macrophage activity is well-validated using ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles and offers a novel clinical approach to assess the effects of anti-inflammatory therapies in human subjects.

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Aims

The authors investigated the anti-inflammatory effects of low- versus high-dose statin therapy on carotid plaque inflammation utilizing noninvasive USPIO-enhanced MRI.

Methods

This prospective, randomized, single-center, double-blind, three-time point molecular MRI trial randomly assigned 47 patients to either low- (10 mg) or high-dose (80 mg) atorvastatin therapy for 12 weeks. Enrolled subjects had clinically documented atherosclerotic carotid disease (>40% stenosis on carotid ultrasound), were statin naïve, or had been on a stable modest statin dosage for more than 4 weeks. Subjects then had to demonstrate signal loss in carotid plaques on baseline USPIO-enhanced MRI (to confirm the presence of carotid plaque inflammation).

For MRI, bilateral multicontrast high-resolution (0.4 mm × 0.4 mm × 3 mm) carotid images were obtained with a 1.5-T scanner using a custom neck coil before USPIO infusion and 36 hours after infusion, at three different time points: baseline, 6 weeks, and 12 weeks after starting therapy. Substantial efforts were made to accurately co-register serial time point images via the peak carotid stenosis and carotid bifurcation. The USPIO compound employed was Sinerem (ferumoxtran-10), administered at a dose of 2.6 mg Fe/kg. Signals were normalized to adjacent sternocleidomastoid signal before and after USPIO in each quadrant of the carotid artery. Signal intensity change (ΔSI) was calculated as signal intensity after USPIO minus signal intensity before infusion. A greater USPIO concentration was identified by stronger signal loss on T2*-weighted MRI due to greater macrophage activity and inflammation. Therefore, a reduction of macrophage activity

will result in a positive change in the ΔSI over time. In addition, to provide a correlative functional readout, cerebral microemboli were assessed using transcranial Doppler in a 5-mm^3 sample volume. Signals were collected for 1-hour intervals.

Results

Of 67 patients assessed for eligibility, 47 met the inclusion criteria and were randomized to high- or low-dose statin therapy for 12 weeks. Seven patients dropped out of the study, leaving 20 subjects in each of the high-and low-dose statin groups. The experimental groups had similar demographic distributions; however, the high-dose group was on average 6 years older. Interobserver agreement was high for USPIO signal changes (interclass coefficient of 0.90).

After 12 weeks, favorable effects were noted in the high- but not low-dose statin group. Specifically, the high-dose group had a significant reduction in the ΔSI (carotid plaque inflammation) at both 6 weeks and 12 weeks compared with baseline. At 6 weeks, the ΔSI for the low-dose group was 0.048, which was not significantly different from baseline, whereas the ΔSI in the high-dose group was 0.131 (P=0.0003 as compared with baseline value of−0.151). Similarly at 12 weeks, the low-dose ΔSI was−0.038 (P=0.3 compared with baseline), whereas the high-dose ΔSI was 0.20 (P<0.0001). In addition to reduced macrophage inflammation, the carotid microemboli count was significantly reduced from baseline in the high-dose group at both 6 and 12 weeks (down 71% and 91%, respectively; P< 0.0001 for each). In contradistinction, microemboli were not significantly different in the low-dose statin group. Other favorable benefits associated with high-dose (but not low-dose) statin therapy included reduced plasma activity of Lp-PLA2, an inflammatory biomarker. As expected, low-density lipoprotein reduction was greater with high-dose therapy (28% reduction at 12 weeks compared with only a 1% reduction in the low-dose statin therapy arm). Presumably, low-dose atorvastatin (10 mg) was similarly potent to baseline statin therapy prior to the start of the study.

Discussion

This is the first randomized, prospective MRI study of the in vivo effects of statins on carotid atherosclerotic inflammation. The authors utilized three—time point serial USPIO-enhanced molecular MRI to detect inflammatory macrophage activity of plaques in only 6 weeks, as opposed to the months to years that may be typically needed to detect changes in plaque volume by anatomical imaging methods. The rapid anti-inflammatory effects noted in the ATHEROMA study shed mechanistic light on the rapid clinical benefits noted in the MIRACL [1] and PROVE-IT [2] trials. The authors also suggested that characterizing the molecular and cellular milieu of atheromata may allow for more timely and economical evaluation of therapeutics in the future. The stated limitations of this study include its relatively small size, the relatively small change in ΔSI that may necessitate dedicated quantitative algorithms for image analysis or be prone to interobserver variability, as well as the fact that two MRI scans (pre- and post-USPIO injection) must be done currently to evaluate ΔSI.

Comments

The medical management of atherosclerosis has made significant progress over the past 20 to 30 years, with large multicenter randomized controlled trials involving hundreds to thousands of patients demonstrating clear survival benefits to pharmacologic therapy. As a result, the standard of care has progressed, and future trials may have to become even larger as the number of clinical events declines due to improved care [3]. Therefore, significant attention has turned to molecular imaging as a method to evaluate novel therapeutics—both in terms of mechanism of action and in terms of surrogate measures of clinical efficacy. For instance, ^{18}fluorodeoxygluose (FDG) positron emission tomography (PET) imaging also recently demonstrated a decrease in plaque inflammation in patients treated with simvastatin [4]. In ATHEROMA, the authors conducted the first prospective randomized trial using macrophage-targeted MRI contrast agent (USPIO) to directly evaluate the biologic effect of high- versus low-dose statin therapy in carotid atherosclerosis. The study successfully demonstrated that a molecular MRI end point (ΔSI) could differentiate the biological anti-inflammatory effects of high-versus low-dose statin therapy. Impressively, the subjects safely underwent three doses of USPIO in a 12-week period, likely one of the first clinical studies to test repeated USPIO administration. An efficient recruitment strategy was employed, namely randomizing only patients demonstrating carotid plaque inflammation at baseline; this form of trial enrichment showcases an important attribute of molecular imaging. Correspondingly, the trial demonstrated a statistically significant effect in both the imaging end point as well as the carotid embolic end point in a matter of weeks with only 20 patients in each arm.

High-dose statin reductions in plaque inflammation correlated with the physiological benefit of reduced carotid emboli, suggesting functional plaque stabilization with high-dose statin therapy. An additional key aspect of this trial was that imaging of plaque inflammation yielded

statistically significant differences far more rapidly than by imaging changes in plaque anatomy, which lags the inflammatory stage of plaque formation [5]. The relatively short time course and small sample size of such a trial could potentially streamline the development of new targeted anti-inflammatory pharmaceuticals, allowing companies and investigators to efficiently design clinical trials to confirm mechanism of action prior to embarking on costly phase 3 clinical trials.

The long-term clinical role of USPIO-enhanced MRI is unclear. Previous studies have demonstrated USPIO particles can be used effectively to image atherosclerosis [6]; however, in the United States these particles are not yet approved for clinical use by the Food and Drug Administration [7], despite the fact that similar compounds have been in development for years [8]. Given the widespread availability of ^{18}FDG, ^{18}FDG-based PET imaging of plaque metabolism/inflammation may predominate for molecular imaging of large-artery atherosclerosis pharmacotherapy, at least in the near term. Nevertheless, from a broader perspective, this trial demonstrates that molecular imaging can be used to evaluate the efficacy of drug therapy, and has the ability to provide lines of evidence complementary to standard clinical trials. The anticipated growth and translation of molecular imaging agents [9] signifies that molecular imaging is likely to play an increasingly important role in the evaluation of new drug therapies. In addition, a final frontier for molecular imaging, namely the coronary arteries, may soon be approachable via intravascular optical imaging catheter technology [10].

Disclosure Dr. Jaffer: Equity interest, Visen Medical.

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