Persistent Anti-Angiogenic Effectiveness in Early Atherosclerosis Following a Single αvβ3-Targeted Administration of Fumagillin Paramagnetic Nanoparticles at 1.5 T

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INTRODUCTION

Although the severity of atherosclerosis in asymptomatic patients may be indirectly suggested by the circulating concentrations of inflammatory markers (i.e., CRP) or lipoproteins (i.e., LDL), direct and noninvasive intramural assessment of the disease spatial heterogeneity and integrated vascular burden may best be quantified with targeted molecular imaging agents. Angiogenesis is an integral feature in the progression of atherosclerosis, which can be delineated with $\alpha_v\beta_3$-integrin targeted nanoparticles. We have previously utilized $\alpha_v\beta_3$-targeted nanoparticles to measure neovascular expansion of the vasa vasorum and to deliver anti-angiogenic therapy (fumagillin) directly to the atherosclerotic plaques. In the current study, we have determined the therapeutic persistence of a single administration of fumagillin-bearing $\alpha_v\beta_3$-targeted paramagnetic nanoparticles.

METHODS

Male New Zealand White rabbits were fed a 0.25% cholesterol diet for 75 days. Transverse black-blood MRI (TR/TE=380/11 ms) of the entire thoracic aorta was performed with a clinical 1.5 T magnet (NT Intera with Master Gradients, Philips Medical Systems, Best, Netherlands) using a quadrature birdcage coil (250 by 250 μm in-plane resolution and 5 mm slice thickness). Images were collected before and four hours after peripheral injection of $\alpha_v\beta_3$-targeted paramagnetic nanoparticles (1 ml/kg) incorporating 0 (n=18) or 0.2 mole% (n=18) fumagillin (30μg/kg), 30 mole% Gd-DTPA-bisoleate, and 0.1mole% anti-vitronectin peptidomimetic homing ligand. Following baseline treatment, half the rabbits within each treatment group remained on the high-cholesterol diet, while the remainder was switched to normal rabbit chow. Aortic vasa vasorum neovasculature was measured in all animals weekly with $\alpha_v\beta_3$-targeted paramagnetic nanoparticles (no drug) over the next four weeks. MRI signal enhancement was calculated from T1-weighted intensities measured before and after paramagnetic nanoparticle injection using a semi-automated image segmentation program.

RESULTS

At baseline, MRI signal enhancement among all cholesterol-fed rabbits across the entire thoracic aorta was 23.9 ± 3.7% and did not differ ($p>0.05$) between fumagillin-treated (25.2 ± 4.9%) and no drug (22.2 ± 6.0%) groups. One week after treatment, MRI enhancement of aortic neovasculature was significantly lower, 5.5 ± 2.7%, in fumagillin-treated animals versus control rabbits, 21.7 ± 4.7% (Figure, $*p<0.05$. The anti-angiogenic effect of a single fumagillin treatment persisted through 2 weeks (Figure, $*p<0.05$), with recrudescence of the neovasculature noted on week 4 (fumagillin: 16.3 ± 3.0 % vs. control rabbits 17.8 ± 2.5%, $p>0.05$). Continuation of cholesterol diets after initial treatment neither altered the effectiveness nor the persistence ($p>0.05$) of fumagillin therapy. Weekly preinjection MR scans revealed no contrast carry-over effect due to repeat molecular imaging with $\alpha_v\beta_3$-targeted paramagnetic nanoparticles. Moreover repetitive administration of $\alpha_v\beta_3$-targeted nanoparticles (no drug) elicited no anti-angiogenic response among the control animals.

CONCLUSIONS

$\alpha_v\beta_3$-targeted paramagnetic nanoparticles provided a non-invasive means to directly quantify early atherosclerotic disease by assessing the extent of neovascular expansion by the vasa vasorum. Furthermore, inclusion of fumagillin into the $\alpha_v\beta_3$-targeted nanoparticles led to an acute anti-neovascular response that persisted for 2 weeks before recrudescing over the remainder of the month. Serial imaging of angiogenesis with $\alpha_v\beta_3$-targeted paramagnetic nanoparticles (no drug) provided quantitative noninvasive assessments of treatment efficacy without associated carry-over contrast effects or therapeutic impact. Continuation of animals on hyperlipidemic diets following initial treatment did not influence either the magnitude or the duration of fumagillin effectiveness. These results suggest that a single systemic administration of $\alpha_v\beta_3$-targeted fumagillin nanoparticles can provide a potent and prolonged antiangiogenic therapy, which in the future could be featured in an aggressive anti-atherosclerosis strategy to stabilize plaque and prevent myocardial infarction or stroke.