Regional Angiogenesis With Vascular Endothelial Growth Factor in Peripheral Arterial Disease

A Phase II Randomized, Double-Blind, Controlled Study of Adenoviral Delivery of Vascular Endothelial Growth Factor 121 in Patients With Disabling Intermittent Claudication

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Background—“Therapeutic angiogenesis” seeks to improve perfusion by the growth of new blood vessels. The Regional Angiogenesis with Vascular Endothelial growth factor (RAVE) trial is the first major randomized study of adenoviral vascular endothelial growth factor (VEGF) gene transfer for the treatment of peripheral artery disease (PAD).

Methods and Results—This phase 2, double-blind, placebo-controlled study was designed to test the efficacy and safety of intramuscular delivery of AdVEGF121, a replication-deficient adenovirus encoding the 121-amino-acid isoform of vascular endothelial growth factor, to the lower extremities of subjects with unilateral PAD. In all, 105 subjects with unilateral exercise-limiting intermittent claudication during 2 qualifying treadmill tests, with peak walking time (PWT) between 1 to 10 minutes, were stratified on the basis of diabetic status and randomized to low-dose (4x10^7 PU) AdVEGF121, high-dose (4x10^8 PU) AdVEGF121, or placebo, administered as 20 intramuscular injections to the index leg in a single session. The primary efficacy end point, change in PWT (ΔPWT) at 12 weeks, did not differ between the placebo (1.8±3.2 minutes), low-dose (1.6±1.9 minutes), and high-dose (1.5±3.1 minutes) groups. Secondary measures, including ΔPWT, ankle-brachial index, claudication onset time, and quality-of-life measures (SF-36 and Walking Impairment Questionnaire), were also similar among groups at 12 and 26 weeks. AdVEGF121 administration was associated with increased peripheral edema.

Conclusions—A single unilateral intramuscular administration of AdVEGF121 was not associated with improved exercise performance or quality of life in this study. This study does not support local delivery of single-dose VEGF121 as a treatment strategy in patients with unilateral PAD. (Circulation. 2003;108:1933-1938.)

Key Words: peripheral vascular disease ■ angiogenesis ■ gene therapy ■ claudication ■ viruses

Therapeutic angiogenesis seeks to improve tissue perfusion through the growth and proliferation of blood vessels in response to delivery of angiogenic cytokines. Angiogenic growth factors may be delivered in the form of protein or gene transfer approaches using viral or plasmid vectors. Local gene transfer to facilitate therapeutic angiogenesis in peripheral arterial disease (PAD) has several inherent advantages compared with protein delivery, including protracted expression of the protein, which may be important in sustenance of the angiogenic response, reduced systemic exposure to growth factors, and ease of delivery to peripheral tissues.

In previous studies involving animal models of hind-limb and coronary ischemia, adenoviral delivery of vascular endo-
thelial growth factor 121 (VEGF121) has been shown to induce angiogenesis and arteriogenesis, as evidenced by improvements in angiographic scores, perfusion, and bioenergetic or contractile reserve.2,3 Small open-label phase 1 angiogenesis trials using such a strategy have demonstrated feasibility and safety in patients with symptomatic PAD4,5 and coronary artery disease.6,7 These studies served as the basis for the Regional Angiogenesis with Vascular Endothelial growth factor trial (RAVE), in which we hypothesized that localized targeting of AdVEGF121 to the muscles of the lower extremity would improve ischemic limb symptoms and walking endurance in patients with symptomatic, predominantly unilateral claudication caused by infraluminal PAD.

Methods

Study Design and End Points

The institutional review board at each participating institution approved the protocol, the procedures followed were in accordance with institutional guidelines, and all patients provided written informed consent before undergoing study-specific procedures. The primary endpoint was change from baseline in peak walking time (ΔPWT) at 12 weeks after treatment. The secondary efficacy variables included ΔPWT at 26 weeks, claudication onset time (COT) at 12 and at 26 weeks, resting and postexercise ankle-brachial index (ABI) in the treated limb at 12 and at 26 weeks, and quality of life (using the Physical Component Summary Scale of the SF-36 Health Survey and Walking Impairment Questionnaire) at 12 and 26 weeks. Safety was evaluated in the study by adverse event monitoring, physical examinations, laboratory tests, resting ECGs, ophthalmological exams, and cancer screens.

Agent Used

AdVEGF121 is an E1a and partially deleted E1b and E3 adenoviral construct based on a replication-deficient adenovirus type 5 vector, carrying the VEGF121 transgene with a cytomegalovirus promoter enhancer, and is identical to that used in previous studies.4,5,7

Patient Population

Male and female subjects between 40 and 80 years of age with PAD (resting ABI <0.8 in the affected limb) and chronic, stable, predominantly unilateral intermittent claudication of ≥6 months’ duration on a stable medication regimen were recruited. Exercise-associated flow limitation (>20% fall in ABI with exercise) and unilateral exercise-limiting claudication, with exercise duration between 1 and 10 minutes (and variability within 20%) on 2 consecutive graded Gardner-Skinner protocols,8 were required for inclusion into the study.

Enrollment Criteria

The study-specific enrollment criterion has been published previously.8 Briefly, study participation required (1) preserved proximal arterial inflow, (2) >50% femoropopliteal stenosis (by radio contrast or magnetic resonance angiography or duplex ultrasound), and (3) at least 1 patent infrapopliteal artery. Exclusionary criteria included contraindications to growth factor delivery, anti-adenoviral IgM titer >1:50, exercise-limiting claudication reported in nonindex leg, or limitation of exercise for any reason other than unilateral claudication.

Study-Specific Procedures

Safety Evaluations

Subjects were assessed for contraindications to angiogenic growth factor exposure, including malignancy and retinal neovascularization. Evaluations included a careful history and assessment in accordance with American Cancer Society guidelines at entry, physical examinations at screening and throughout study follow-up, chest x-ray and rest ECGs at entry and at 12 weeks of follow-up, and assessment for the presence of diabetic retinopathy at entry and at 26 weeks of follow-up. Retinal exams were performed by on-site ophthalmologists using standardized protocols.8,9 For all diabetic patients and in cases of suspected proliferative retinopathy, standard field stereo color fundus photographs were sent to a central core laboratory for evaluation. Laboratory parameters included sequential urinalyses and serum hematologic, chemistries (renal, liver, and muscle function), and coagulation at screening and at weeks 1, 6, and 26. For a subset of patients in the 3 groups (n=24), plasma AdVEGF121 levels were determined by polymerase chain reaction 24 hours after dosing. Anti-adenoviral IgM titers and neutralizing antibody titers against adenovirus type 5 were analyzed for all patients at baseline by use of a standard assay. Urine and throat swabs for adenoviral cultures were collected at week 2 for a subset of patients.

Efficacy Assessments

Two consecutive graded Gardner-Skinner protocol exercise tolerance tests were performed before entry and at weeks 12 and 26. PWT was defined as the maximum time the subject was able to walk on the treadmill, and the onset of ischemic calf discomfort in the symptomatic leg was recorded as COT. ABI was recorded at rest and 1 minute after exercise at baseline and weeks 12 and 26. Quality-of-life measures (Walking Impairment Questionnaire and SF-36) were administered before entry and at weeks 12 and 26.

Study Drug Administration

Patients were stratified according to diabetic status and then randomized to receive either placebo (vehicle alone containing Tris, magnesium hydrochloride, sodium chloride, and sucrose) or low-dose (4×109 particle units [PU]) or high-dose (4×1010 PU) AdVEGF121. The delivery location was standardized as described previously, and the study drug was administered as twenty 1-mL injections, separated by 1.5 to 2.0 cm both anteriorly and posteriorly.8 Briefly, on the basis of the anatomic pattern of PAD, injections were delivered in the lower thigh region (when the distal superficial femoral artery and popliteal artery were patent) or into the lower thigh and upper calf region (when the distal superficial femoral artery and popliteal artery were occluded).

Sample Size Estimates and Statistical Plan

A sample size of 35 patients in each treatment arm was estimated to provide 80% power to detect a mean difference of 1.5 minutes in ΔPWT between either of the 2 treatment groups and placebo, assuming the SD for ΔPWT to be 2 minutes. Data were analyzed by use of an intention-to-treat analysis (ITT), in which missing data were analyzed using the last observation carried forward procedure, and PWT and COT were recorded as 0 at evaluations, after progression of disease requiring mechanical intervention or resulting in inability to walk on the treadmill. A modified ITT (MITT) approach was also used for the primary and secondary efficacy analyses and was conducted on data from all patients who had baseline and ≥1 postrandomization assessments. In the MITT analysis, missing data and data collected after revascularization or treatment with cilostazol were excluded. All statistical tests were 2-sided and were conducted at an overall significance of 0.05. In addition, an ANCOVA was used to compare the effects of 2 doses of AdVEGF121 and placebo on the primary end point with diabetic status and baseline walking time as covariates.

Results

Patient Demographics

A total of 105 subjects were randomized and received placebo, 4×109 PU AdVEGF121, or 4×1010 PU AdVEGF121 (Figure 1). Table 1 summarizes the baseline demographic and risk factor profile of subjects assigned to the treatment groups. There were no significant differences in medication use between the 3 groups with respect to statins...
(67% in placebo and 61% in the AdVEGF121 groups), ACE inhibitors (36% in placebo and 43% in the AdVEGF121 groups), antithrombotic therapy (aspirin, 67% in the placebo group and 70% in the AdVEGF121 groups; clopidogrel, 6% in the placebo and 18% in the AdVEGF121 groups) and β-blockers (6% each in the placebo and AdVEGF121 groups). Baseline resting ABIs of the index leg were identical in the 3 groups (Table 2 and Figure 2). Resting ABIs of the nonindex leg were 0.8±0.2, 0.9±0.2, and 0.9±0.2 in the placebo, low-dose, and high-dose groups, respectively. At entry, PWT and COT and postexercise ABIs were comparable across groups (Table 2).

**TABLE 1. Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (n=33)</th>
<th>AdVEGF121 4×10^19 PU (n=32)</th>
<th>AdVEGF121 4×10^20 PU (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>68±10</td>
<td>66±9</td>
<td>64±9</td>
</tr>
<tr>
<td>Female</td>
<td>3 (9)*</td>
<td>6 (19)</td>
<td>13 (33)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (85)</td>
<td>24 (75)</td>
<td>31 (78)</td>
</tr>
<tr>
<td>Hyperlipidemia (LDL &gt;130 mg/dL)</td>
<td>10 (30)</td>
<td>6 (19)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Dyslipidemia (HDL ≤35 mg/dL)</td>
<td>8 (24)</td>
<td>6 (19)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>20 (61)</td>
<td>11 (35)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Smoker, current</td>
<td>11 (33)</td>
<td>6 (19)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>No exercise (sedentary)</td>
<td>19 (58)</td>
<td>14 (44)*</td>
<td>31 (78)*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (27)</td>
<td>8 (25)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Previous LE revascularization, surgical</td>
<td>12 (36)</td>
<td>14 (44)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Previous LE revascularization, percutaneous</td>
<td>11 (33)</td>
<td>11 (34)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Previous LE revascularization, all</td>
<td>18 (55)</td>
<td>20 (63)</td>
<td>22 (55)</td>
</tr>
<tr>
<td>SFA disease</td>
<td>32 (97)</td>
<td>32 (100)</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

Values are given as number (%) of patients, with the exception of age, which is given as mean±SD. LE indicates lower extremity; SFA, superficial femoral artery.

*Statistically significant difference between groups (Fisher’s exact test, P<0.05)

**Safety of AdVEGF121**

Adverse events are summarized in Table 3. Edema of the injected extremity was more common in the high-dose group than the placebo and low-dose groups, whereas edema of the contralateral limb was not reported by any subject within 30 days of administration. Lower-extremity revascularization procedures were distributed roughly equally in the 3 arms, and none occurred in the AdVEGF121 groups within 90 days. Two amputations followed unsuccessful attempts at surgical revascularization: 1 in the placebo (day 114) and 1 in the high-dose (day 293) group. Cardiovascular events (death, myocardial infarction, stroke, or revascularization) occurred in 2 patients in the placebo group (both were transient ischemic attacks, on days 6 and 83), in 1 patient in the low-dose group (right thalamic infarct on day 352), and in 1 patient in the high-dose group (acute myocardial infarction on day 253).

**TABLE 2. PWT and COT at 12 and 26 Weeks in the Index Extremity**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=33)</th>
<th>AdVEGF121 4×10^19 PU (n=32)</th>
<th>AdVEGF121 4×10^20 PU (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PWT, min</td>
<td>5.0±3.0</td>
<td>4.5±2.2</td>
<td>4.3±1.9</td>
</tr>
<tr>
<td>Baseline COT, min</td>
<td>2.0±1.4</td>
<td>2.0±1.1</td>
<td>1.9±1.2</td>
</tr>
<tr>
<td>Resting ABI (index leg)</td>
<td>0.6±0.2</td>
<td>0.6±0.1</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>Postexercise ABI (index leg)</td>
<td>0.4±0.1</td>
<td>0.3±0.2</td>
<td>0.4±0.2</td>
</tr>
<tr>
<td><strong>Week 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔPWT</td>
<td>1.8±3.2</td>
<td>1.6±1.9</td>
<td>1.5±3.1</td>
</tr>
<tr>
<td>ΔCOT</td>
<td>1.8±3.3</td>
<td>1.2±2.0</td>
<td>1.0±2.2</td>
</tr>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔPWT</td>
<td>2.7±4.9</td>
<td>1.1±1.7</td>
<td>2.6±3.8</td>
</tr>
<tr>
<td>ΔCOT</td>
<td>3.1±4.7</td>
<td>1.2±1.9</td>
<td>1.7±3.8</td>
</tr>
</tbody>
</table>

MITT analysis. Data are absolute value in minutes ± SD by least-squares mean.
One patient who received placebo died of ovarian cancer diagnosed on day 76. In total, there were 3 malignancies, including the placebo patient described above and 2 additional cases in the high-dose AdVEGF121 group: a basal cell skin cancer diagnosed at 1 year and a bladder cancer diagnosed on day 199. There were 3 cases of ocular neovascularization in the trial, including neovascularization in the iris of a diabetic patient who received placebo, and 2 cases of a single new microaneurysm (background retinopathy) in the low-dose group were reported at the week 26 follow-up visit by the site ophthalmologists; however, both of the cases in the low-dose group were also evaluated by the core laboratory and were not considered to represent worsening proliferative retinopathy. There were no additional adverse events of concern.

Adenoviral cultures of urine and throat swabs for 12 AdVEGF121-treated patients were all negative at week 2, indicating that the virus was indeed replication deficient.

Circulating AdVEGF121 was noted in 75% of individuals in the high-dose group 24 hours after dosing (6 of 8 individuals in this cohort), whereas no individuals in the low-dose (0 of 8) or the placebo (0 of 8) group had detectable levels 24 hours after administration.

**Efficacy End Points**

Data reported are for the MITT analysis. Although all groups demonstrated improvements in the primary end point of ΔPWT at 12 weeks (Table 2), there was no difference between groups (Figure 3 and Table 2). Logarithmic transformation of PWT values did not appreciably alter these findings. Similarly, there was no difference in COT or ABI in the AdVEGF121 groups compared with placebo at either the 12-week or the 26-week time point (Figure 2 and Table 2). Results of ITT analysis were no different.

There was improvement in all of the individual components of the WIQ questionnaire in the low-dose and high-dose AdVEGF121 groups up to week 12 (Table 4); however, the magnitude of improvement was identical to that in the placebo group. No further improvement was noted at week 26. Similarly, there were no differences in the individual component scores of the SF-36 at either the 12- or 26-week end point in any of the AdVEGF121 cohorts above what was observed in the placebo group (data not shown).

**TABLE 4. Walking Impairment Questionnaire at Weeks 12 and 26**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=33)</th>
<th>AdVEGF121 4×10^6 PU (n=32)</th>
<th>AdVEGF121 4×10^10 PU (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIQ claudication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27.5±16.5</td>
<td>34.4±20.8</td>
<td>33.3±27.1</td>
</tr>
<tr>
<td>Week 12</td>
<td>41.7±31.7</td>
<td>44.5±26.7</td>
<td>46.8±29.9</td>
</tr>
<tr>
<td>Week 26</td>
<td>44.8±25.3</td>
<td>50.0±23.7</td>
<td>44.4±30.7</td>
</tr>
<tr>
<td>WIQ distance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.4±15.0</td>
<td>15.2±16.5</td>
<td>12.6±14.7</td>
</tr>
<tr>
<td>Week 12</td>
<td>29.5±25.4</td>
<td>29.1±29.8</td>
<td>22.9±22.9</td>
</tr>
<tr>
<td>Week 26</td>
<td>28.0±26.2</td>
<td>31.0±26.5</td>
<td>29.5±30.3</td>
</tr>
<tr>
<td>WIQ speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>19.5±19.0</td>
<td>21.6±15.9</td>
<td>19.3±20.3</td>
</tr>
<tr>
<td>Week 12</td>
<td>30.9±22.4</td>
<td>33.1±25.1</td>
<td>25.9±22.0</td>
</tr>
<tr>
<td>Week 26</td>
<td>30.1±23.9</td>
<td>35.7±23.6</td>
<td>29.2±26.5</td>
</tr>
<tr>
<td>WIQ stair climbing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.2±22.4</td>
<td>39.5±26.0</td>
<td>23.5±20.2</td>
</tr>
<tr>
<td>Week 12</td>
<td>43.1±30.5</td>
<td>49.1±30.2</td>
<td>36.5±24.8</td>
</tr>
<tr>
<td>Week 26</td>
<td>42.9±31.0</td>
<td>47.5±29.5</td>
<td>44.1±32.9</td>
</tr>
</tbody>
</table>

MITT analysis. Data are mean±SD. WIQ indicates Walking Impairment Questionnaire.

*Pairwise comparison with baseline.
involved individuals with bilateral disease. The majority of placebo-controlled trials in claudication have demonstrated an increase in the placebo group of 0.60 to 1.0 minutes. Baseline Ad titers did not correlate with responses to AdVEGF121 (data not shown).

**Discussion**

RAVE is the first randomized placebo-controlled trial to test adenoviral gene transfer of VEGF to the lower extremities in individuals with PAD. The major finding of this study is that a single intramuscular delivery of AdVEGF121 at doses of $4 \times 10^9$ and $4 \times 10^{10}$ PU resulted in changes in walking times and quality-of-life measures that were comparable to placebo in patients with intermittent claudication. The RAVE study targeted a homogeneous population with femoropopliteal disease, which was managed predominantly medically. Enrolled subjects had a finite range of PWTs (between 1 and 10 minutes) and thus were significantly impaired but not unstable. Randomization was stratified by diabetic status, whereas baseline comorbidities and therapies that are known to potentially enhance or attenuate angiogenic responsiveness were equally distributed across groups. A somewhat unusual feature of RAVE was the deliberate selection of patients with predominantly unilateral symptoms (and probably disease), because the delivery was unilateral. This was intended to reduce the possibility that symptoms in the contralateral untreated extremity might mask any treadmill benefit that could have occurred in the treated extremity. The majority of placebo-controlled trials in claudication have involved individuals with bilateral disease. Because PAD is generally bilateral in anatomic distribution, the presence of unilaterally severe symptoms may reflect a patient population different from that typically encountered. RAVE had a larger than anticipated change in walking time and quality-of-life measures in the placebo group, and this may potentially have limited our ability to discern a benefit in the AdVEGF121 groups. The extent of improvement noted in this trial in the placebo group is in contrast to that of other trials, which have demonstrated an increase in the placebo group of 0.60 to 1.0 minutes.

There are additional reasons that could have contributed to the lack of treatment effect noted in this study. It has been suggested that the duration of expression of the VEGF transgene using adenoviral approaches (1 to 2 weeks) may be insufficient to induce phenotypic changes necessary for long-term sustained improvements in perfusion that may be needed to discern improvements in walking ability; however, these studies have involved primarily nonischemic models. Thus, the optimal dose and duration of VEGF expression for the promotion of angiogenesis in the clinical setting is as yet unclear. It is conceivable that prolongation of VEGF expression using a repeat dosing strategy may obviate the limitations of short-term expression. The lack of change in ABI in the AdVEGF121-treated patients may reflect a true lack of improvement in lower-extremity perfusion despite the change in walking time. Interestingly, the placebo group of the TRAFFIC study had no change in ABI at 90 days, whereas the patients treated with fibroblast growth factor protein had a statistically greater mean increase in PWT and a small but statistically significant improvement in ABI at 90 days.

The efficiency of gene transfer with adenoviruses in adult skeletal muscle remains in question. In contrast to myocardial cells, skeletal muscle cells are relatively difficult to transduce because of lower concentrations of the Coxsackie adenoviral receptor and the presence of physical barriers to transfection such as muscle fascicles and connective tissue. This difference in transfection efficiency with adenovirus between the myocardium and skeletal muscle could potentially explain the results with adenovirus-mediated delivery of VEGF in the myocardium. Limited transfection of target cells within skeletal muscle with expression localized to the site of delivery (lower thigh and/or upper calf), baseline cohort differences (sex and sedentary status differences), and age- and risk factor–dependent decreases in angiogenic efficiency may further undermine angiogenic efficiency. Finally, the results of this trial follow other angiogenesis trials with VEGF in which evidence of success in animal models may not necessarily translate into success in human protocols.

Although safety has been a concern in gene therapy trials, no major safety issues associated with AdVEGF121 were identified throughout 1 year of follow-up. AdVEGF121 gene transfer was associated with increased incidence of lower-extremity edema, indicative of either a biological effect of the growth factor (enhanced permeability) or an inflammatory response to the virus itself.

RAVE is the largest placebo-controlled human adenoviral gene transfer study completed to date. Data from this trial will be helpful for future angiogenesis studies in the selection of the agent, patient population, and outcome measures in the quest for optimal angiogenic strategies that result in the growth of functional blood vessels and improvement in clinical symptoms.

**Core Laboratories**

Ophthalmology Core: University of Wisconsin, Madison.
ECG Core: St Louis University, St Louis, Mo.
Clinical Safety Laboratory Core: MRL International Inc, Highland Heights, Ky.
Viral Studies: Performed at Pfizer Global Research Laboratories, Ann Arbor, Mich, and Viromed Laboratories, Minnetonka, Minn.
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References


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