Intracoronary Basic Fibroblast Growth Factor (FGF-2) in Patients With Severe Ischemic Heart Disease: Results of a Phase I Open-Label Dose Escalation Study

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OBJECTIVES Evaluate the safety, tolerability and preliminary efficacy of intracoronary (IC) basic fibroblast growth factor (bFGF, FGF-2).

BACKGROUND FGF-2 is a heparin-binding growth factor capable of inducing functionally significant angiogenesis in animal models of myocardial ischemia.

METHODS Phase I, open-label dose-escalation study of FGF-2 administered as a single 20-min infusion in patients with ischemic heart disease not amenable to treatment with CABG or PTCA.

RESULTS Fifty-two patients enrolled in this study received IC FGF-2 (0.33 to 48 μg/kg). Hypotension was dose-dependent and dose-limiting, with 36 μg/kg being the maximally tolerated dose. Four patients died and four patients had non-Q-wave myocardial infarctions. Laboratory parameters and retinal examinations showed mild and mainly transient changes during the 6-month follow-up. There was an improvement in quality of life as assessed by Seattle Angina Questionnaire and improvement in exercise tolerance as assessed by treadmill exercise testing (510 ± 24 s at baseline, 561 ± 26 s at day 29 [p = 0.023], 609 ± 26 s at day 57 [p < 0.001], and 633 ± 24 s at day 180 [p < 0.001]), overall p < 0.001). Magnetic resonance (MR) imaging showed increased regional wall thickening (baseline: 34 ± 1.7%, day 29: 38.7 ± 1.9% [p = 0.006], day 57: 41.4 ± 1.9% [p < 0.001], and day 180: 42.0 ± 2.3% [p < 0.001], overall p = 0.001) and a reduction in the extent of the ischemic area at all time points compared with baseline.

CONCLUSIONS Intracoronary administration of rFGF-2 appears safe and is well tolerated over a 100-fold dose range (0.33 to 0.36 μg/kg). Preliminary evidence of efficacy is tempered by the open-label uncontrolled design of the study. (J Am Coll Cardiol 2000;36:2132–9) © 2000 by the American College of Cardiology

Despite recent advances in the treatment of coronary artery disease (CAD), a significant number of patients cannot be adequately managed by either medical therapy or by currently available revascularization procedures including percutaneous transluminal angioplasty (PTCA) and coronary artery bypass surgery (CABG) (1,2). An alternative treatment strategy is therefore warranted in these patients both to control symptoms and improve quality of life, as well as to alter the natural course of advanced ischemic heart disease. Therapeutic angiogenesis may serve that role by altering the natural course of advanced ischemic heart disease (4–5).

Angiogenesis is a complex process that involves endothelial cell migration and proliferation, extracellular matrix breakdown, attraction of pericytes and macrophages, smooth muscle cell proliferation and migration, formation and “sealing” of new vascular structures, and deposition of new matrix (6–8). A number of growth factors, including the fibroblast growth factors (FGF) and vascular endothelial growth factors (VEGF) are integrally involved in the angiogenic response in ischemic conditions and in certain pathological states (6). The availability of these factors has led to studies, which have demonstrated a therapeutic benefit in various animal models of acute and chronic myocardial ischemia (4,5,9). In particular, basic fibroblast growth factor (bFGF, FGF-2) is an attractive candidate as an agent for therapeutic angiogenesis.

FGF-2, a 16.5 kD 146 amino acid heparin-binding protein, is a pluripotent mitogen capable of stimulating migration and proliferation of a variety of cell types including fibroblasts, macrophages, smooth muscle and endothelial cells (10). In addition to these mitogenic properties, FGF-2 can stimulate endothelial production of various proteases, including plasminogen activator and matrix metalloproteinases, induce significant vasodilation through stimulation of nitric oxide release (11,12) and promote chemotaxis. FGF-2 is present in the normal myocardium (13) and its expression is potentiated by hypoxia (14,15) or hemodynamic stress (16). Because of its heparin-binding
properties, FGF-2 binds avidly (Kd 10^{-9} M) to endothelial cell surface heparan sulfates (17). This interaction serves to prolong effective tissue half-life of the FGF-2 protein (18), facilitates its binding to its high-affinity receptors (19) and plays a key role in stimulation of cell proliferation and migration (20,21).

A number of studies have demonstrated the ability of FGF-2 to induce functionally significant angiogenesis in several different animal models of myocardial ischemia. Intracoronary (IC) injections of FGF-2 in the setting of acute coronary thrombosis in dogs or pigs lead to significantly higher vessel counts and reduction in infarct size in growth factor-treated animals compared with controls (22–24). Continuous administration of FGF-2 in the setting of chronic ischemia, either directly into the occluded coronary artery or into the left atrium, resulted in augmentation of coronary flow in the growth factor-treated animals (25,26). Sustained release perivascular administration or intrapericardial delivery of FGF-2 not only improved myocardial blood flow in the ischemic myocardium but also improved regional left ventricular function in the ischemic zone (9,27,28).

Single bolus IC administration of FGF-2 has obvious practical advantages compared with administration of sustained-release preparations or multiple repetitive injections. We therefore conducted a Phase I, open-label dose-escalation study of intracoronary FGF-2 in patients with severe ischemic heart disease in order to determine the maximally tolerated dose (MTD) and to evaluate feasibility, safety and preliminary efficacy of this mode of therapy. Herein, we report the acute results and six months follow-up data.

METHODS

Patient selection. The study was conducted at two centers, the Beth Israel Deaconess Medical Center (Boston, Massachusetts) and Emory University Hospital (Atlanta, Georgia), and patients were enrolled between December 1997 and July 1998. The study was approved by the Institutional Review Boards at both hospitals. The inclusion criteria selected for patients with advanced CAD with inducible ischemia and who were considered to be suboptimal candidates for either PTCA or CABG. Patients were excluded from the study if they had any of the following criteria: uncompensated congestive heart failure or an ejection fraction <20%; a myocardial infarction within three months; new onset of angina or unstable angina within three weeks; PTCA, CABG, stroke or transient ischemic attack within six months; uncontrolled hemodynamically significant arrhythmias; critical valvular disease; restrictive or hypertrophic cardiomyopathy; arteriovenous malformations; proliferative retinopathy, retinal vein occlusion, or macular edema; renal insufficiency (creatinine clearance < 80 ml/min by 24-h urine collection); vasculitis or chronic immunosuppressive therapy; or any malignancy within the past 10 years (except for curatively treated nonmelanoma skin cancer). Patients with diabetes mellitus were eligible if they had no proliferative retinopathy or severe nonproliferative retinopathy, and no microalbuminuria.

Study design. This was an open-label interpatient dose escalation study. The initial dose of 0.33 µg/kg was escalated over eight sequential groups to 48 µg/kg IC. At least four patients were studied at each dose. If no patient experienced dose-limiting toxicity as defined by the protocol within six days, the dose was escalated; if one patient experienced dose-limiting toxicity, an additional four patients were studied at that dose. The MTD was defined as the dose tolerated by 9 of 10 patients.

Study procedures. After providing informed consent and meeting all eligibility criteria, patients underwent baseline evaluations that included a complete medical history and physical examination, an ophthalmologic examination with fundus photography read by a core laboratory using the Early Treatment Diabetic Retinopathy score (ETDRS), an exercise tolerance test (ETT), a Seattle Angina Questionnaire (SAQ) (29,30), and nuclear and MRI cardiac scans. Measurement of initial health status allowed the use of change in scores, thus adjusting for differences in baseline health. Self-administration was used instead of telephone interview to minimize data collection bias (29,30).

On day 1, patients underwent right and left heart catheterization and coronary angiography. If the coronary anatomy was not amenable to PTCA or CABG, recombinant FGF-2 (rFGF-2, Chiron Corporation, Emeryville, CA) was infused with a Baxter pump through diagnostic catheters into two major conduits of myocardial blood supply over 20 min (10 min in each vessel) with continuous monitoring of systemic blood pressure and right atrial and pulmonary capillary wedge pressures, and cardiac output. In occasional patients the entire dose was infused into a single vessel that was believed to be the major source of blood supply. Prior to initiation of rFGF-2 infusion, normal saline was administered intravenously (IV), if required, to ensure mean pulmonary capillary wedge pressure >12 mm Hg. Heparin (40 U/kg) was administered IV more than 10 min before rFGF-2. The volume of infusion varied with dose and the patient’s weight, ranging from 10 ml at lower doses to 40 ml at higher doses.
The right heart (Swan–Ganz) catheter was left in place for 7 h following drug infusion to monitor filling pressures and cardiac output. Patients were monitored with full-disclosure telemetry for 24 h following rFGF-2 administration. Patients were discharged 24 h after study drug infusion and clinical follow-up visits were performed at days 6, 15, 29, 57, 180 and 360. Quality of life was assessed using the Seattle Angina Questionnaire at baseline and days 57 and 180. ETTs were obtained at days 29, 57 and 180. Exercise stress nuclear perfusion scans (rest thallium/stress 99mTc-sestamibi) and resting cardiac magnetic resonance scans were performed at days 29, 57 and 180.

Safety assessment. The safety of intracoronary rFGF-2 was assessed through clinical observations, electrocardiography, hemodynamic monitoring, hematologic and serum chemistry profiles, development of anti-rFGF-2 antibodies, detailed ophthalmological exams with fundus photography and assessment of renal function by determination of creatinine clearance and proteinuria using 24-h urine collection.

Dose-limiting toxicity was predefined as persistent (>10 min) drop in systolic blood pressure by >50 mm Hg, change in heart rate to >120/min or to <50/min, new clinically significant arrhythmia, new ischemic symptoms or ECG changes, new congestive heart failure, deterioration in renal function or any other serious adverse events.

Magnetic resonance (MR) imaging. Magnetic resonance (MR) imaging was performed at baseline and days 29, 57 and 180 in the body coil of a 1.5 T whole-body Siemens Vision or Phillips NT system. Functional imaging was performed during breath-hold using shared-center FLASH or multishot echoplanar imaging in each of the three mutually perpendicular standard views, producing 16–24 sequential image frames each, collected over approximately 12 heartbeats to measure regional wall systolic thickening. MR blood arrival imaging was assessed as previously described (31). A series of four inversion recovery images was obtained with the inversion time (TI) adjusted to minimize signal intensity from myocardium. Using the best TI for nulling myocardial signal, a series of concurrent parallel images were acquired in diastole during breathhold, at baseline and after the bolus injection of contrast media (0.05 mmol/kg gadopentetate) (31,32). Measurement of the timing of half-maximum signal arriving in the different parts of the myocardium demonstrated the existence of several distinct regions, including normal myocardium and areas exhibiting delayed contrast arrival (ischemic zones). For each scan, a space-time map demonstrating distribution of contrast signal density over the left ventricular wall as a function of time was created. The extent of the territory demonstrating delayed arrival of contrast, defined as >1-s delay of contrast density reaching its 50% maximum value reflecting the most severely hypoperfused part of the myocardium, was then calculated and expressed as percent of the total left ventricular myocardial area (31). MR analysis was performed by a core lab blinded to rFGF-2 dose assignment and to study sequence.

Statistical methods. Data are pooled for all dose groups. Baseline characteristics and acute hemodynamic parameters are expressed as mean ± standard deviation. Efficacy variables were analyzed using a linear mixed effects model with an unstructured covariance assumption for the repeated measurements, fit using the restricted maximum likelihood method. Model-based estimates of the means ± standard errors (SEM) are presented. An overall F-test for equality across all time points was conducted first. If this initial test was statistically significant, pairwise t tests to compare baseline with each on-study time point were performed at the nominal α-level. All reported p-values are two-sided, and a p-value < 0.05 was considered statistically significant.

RESULTS

Patient population. Fifty-two patients met all eligibility criteria and received a single IC infusion of rFGF-2. Their baseline characteristics are summarized in Table 1. The mean age was 60.8 ± 10.1 years (range 41 to 80) and 2 of 52 patients were women. Six patients (11%) had diabetes mellitus and 31 patients (60%) had elevated cholesterol (serum cholesterol > 200 mg/dl). Forty-three patients (83%) had a history of at least one prior CABG. The mean ejection fraction (evaluated by MR imaging) was 51.4 ± 12.0 (range 20–73).

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Characteristics</th>
<th>All Patients (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.8 ± 10.1</td>
</tr>
<tr>
<td>Men/women</td>
<td>50/2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (42%)</td>
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<tr>
<td>Elevated cholesterol*</td>
<td>31 (60%)</td>
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<tr>
<td>Prior CABG</td>
<td>43 (83%)</td>
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<tr>
<td>Multiple prior CABG (2 or 3)</td>
<td>12 (23%)</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>26 (50%)</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>11 (21%)</td>
</tr>
<tr>
<td>Class II</td>
<td>25 (48%)</td>
</tr>
<tr>
<td>Class III</td>
<td>11 (21%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Ejection fraction by MR analysis (%)</td>
<td>51.4 ± 12.0 (range 20–73)</td>
</tr>
</tbody>
</table>

*Serum cholesterol > 200 mg/dl.

CABG = coronary artery bypass grafting; EF = ejection fraction; PTCA = percutaneous transluminal coronary angioplasty, MR = magnetic resonance imaging.

Acute results. The doses of rFGF-2 studied ranged from 0.33 μg/kg (based on ideal body weight) to 48 μg/kg and are summarized in Table 2; the entire dose was administered in each case. Two patients in the 48 μg/kg group had hypotension. At 36 μg/kg, only one of 10 patients developed dose-limiting toxicity (leucocytosis and nausea delaying discharge); this led to the designation of 36 μg/kg as the MTD. Overall, there were no clinically significant
hemodynamic effects even at the highest doses. The mean arterial pressure was 96.0 ± 10.5 mm Hg at baseline, 90.0 ± 13.1 mm Hg during the infusion, and 86.3 ± 9.6 mm Hg at 7 h.

Clinical follow-up and safety assessment. Clinical follow-up of at least six months was obtained on all patients. A total of 30 serious adverse events were reported in 22 patients (Table 2). There was no apparent relationship between increasing dose of rFGF-2 and serious adverse events.

Four patients died. Two deaths were sudden and occurred 22 days (0.65 μg/kg dose, EF 30%) and 114 days (48 μg/kg dose, EF 22%) after rFGF-2 infusion. One patient (2 μg/kg) died 72 days after rFGF-2 infusion from complications of cardiac transplantation after sustaining several myocardial infarctions beginning four days after drug infusion. One patient with preexisting lymphadenopathy (6 μg/kg) died at 62 days from septic complications of large-cell lymphoma, which was diagnosed at 10 days after dosing. In retrospect, the lymphoma most likely predated rFGF-2 infusion. One additional patient was diagnosed with metastatic adenocarcinoma to the liver at day 431. Four patients had non-Q-wave myocardial infarctions at days 5 (2 μg/kg dose group), 68 (6 μg/kg), 132 (0.33 μg/kg) and 146 (48 μg/kg). Four patients had revascularization procedures (CABG and aortic valve replacement in one patient at day 68 [6 μg/kg] and PTCA in three patients at day 100 [0.33 μg/kg], 290 [24 μg/kg], and 223 [48 μg/kg]). One patient developed atrial fibrillation at day 37. The most commonly reported (>10% of patients) adverse events were asthenia (19%), chest pain (19%), hypotension (15%), dyspnea (13%), insomnia (13%), angina (12%) and palpitations (12%). Of these asthenia, hypotension, insomnia, and dyspnea were more common at higher doses. No patients withdrew from the study because of adverse events. Transient leukocytosis was observed in half the patients at ≥24 μg/kg. Fluctuations in renal function occurred but were transient and not dose related. Proteinuria (>250 mg/24 h) occurred in four patients (7.8%). Ophthalmological exams with fundus photography at baseline and day 57 were available for 45 patients; seven patients lacked either baseline or 57-day assessments. Forty patients (89%) showed no change from baseline, two patients improved by two ETDRS grades and three patients worsened by two grades (0.65, 2.0 and 36.0 μg/kg groups).

The presence of anti-rFGF-2 antibodies was assessed at baseline and days 15, 57 and 180. There were no clinically significant changes in antibody titers.

Quality of life assessment. There were significant improvements in all five scales of the Seattle Angina Questionnaire at days 57 and 180, as compared with baseline (Fig. 1). In particular, angina frequency score increased (denoting improvement) from 39.8 ± 3.8 at baseline to 68.8 ± 4.0 (p < 0.001) at day 57 and 64.7 ± 4.5 at day 180 (p < 0.001), overall p < 0.001. Exertional capacity score

<table>
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<tr>
<th>Dose Group (μg/kg)</th>
<th>Patients Dosed (n)</th>
<th>Related Events (n)</th>
<th>Unrelated Events (n)</th>
<th>Total Events (patients)</th>
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<tbody>
<tr>
<td>0.33</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>8 (3)</td>
</tr>
<tr>
<td>0.65</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3 (2)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>5 (3)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2 (2)</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2 (2)</td>
</tr>
<tr>
<td>24</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>3 (3)</td>
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<tr>
<td>36†</td>
<td>10†</td>
<td>2</td>
<td>1</td>
<td>3 (3)</td>
</tr>
<tr>
<td>48†</td>
<td>10†</td>
<td>2</td>
<td>1</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>14</td>
<td>15</td>
<td>30 (22)</td>
</tr>
</tbody>
</table>

*Ideal body weight. †Two patients in 48 μg/kg group (#4 and #10) experienced dose-limiting toxicities (one patient had hypotension lasting >10 minutes and one patient had orthostatic hypotension which delayed discharge). Only 1 of 10 patients at 36 μg/kg had significant toxicity (leukocytosis and nausea delaying discharge).
increased from 49.2 ± 2.8 at baseline to 64.5 ± 3.1 at day 57 (p < 0.001) and 73.0 ± 3.8 at day 180 (p < 0.001), overall p < 0.001.

Exercise treadmill testing. A subset of patients with matching baseline and follow-up exercise treadmill protocols was selected for analysis (Fig. 2). Among this group, the mean exercise time improved from 510 ± 24 s at baseline (n = 35) to 561 ± 26 s at day 29 (n = 28; p = 0.023), 609 ± 26 s at day 57 (n = 31; p < 0.001), and 633 ± 24 s at day 180 (n = 23; p < 0.001).

Left ventricular function assessment. Magnetic resonance imaging was performed in 51 patients at baseline and was repeated at days 29 (n = 47), 57 (n = 45) and 180 (n = 31) to assess resting left ventricular ejection fraction, regional wall motion, and myocardial contrast arrival. There was a small improvement in overall left ventricular ejection fraction over the course of the study (baseline 51.4 ± 1.7%, day 29: 54.2 ± 1.7% [p = 0.02], day 57: 55.2 ± 1.9% [p = 0.003], day 180: 57.2 ± 1.7% [p < 0.001], overall p = 0.002). The hypoperfused target area was selected for assessing regional left ventricular wall motion analysis. Systolic thickening of this area (target wall) and normal wall were measured using a semiautomated quantification algorithm of short-axis MR images. Resting normal wall systolic thickening was 46.1 ± 1.6% at baseline and did not change significantly throughout the study duration (p = 0.16). Resting target wall thickening was significantly lower than normal wall thickening at baseline (34.0 ± 1.7% vs. 46.1 ± 1.6%, p < 0.001). Target wall thickening significantly improved at days 29, 57, and 180 as compared to baseline [baseline: 34 ± 1.7%, day 29: 38.7 ± 1.9% (p = 0.006), day 57: 41.4 ± 1.9% (p < 0.001), and day 180: 42.0 ± 2.3% (p < 0.001), overall p = 0.001] (Fig. 3).

Myocardial perfusion assessment. Myocardial perfusion was assessed using MR imaging (Fig. 4). The mean size of the delayed contrast arrival zone was 15.4 ± 0.8% of the left ventricle at baseline and was similar to the global left ventricular extent of ischemia determined by nuclear perfusion imaging (17.3 ± 1.8%). The size of the myocardial area demonstrating delayed contrast arrival was significantly reduced from baseline (15.4 ± 0.8%) at day 29 (9.0 ± 0.6%, p < 0.001), day 57 (5.6 ± 0.7%, p < 0.001) and day 180 (4.9 ± 0.8%, p < 0.001), overall p < 0.001.

There was no correlation between the dose used and the various efficacy parameters studied.

**DISCUSSION**

In this Phase I trial, safety, tolerability and preliminary efficacy of a single intracoronary infusion of rFGF-2 were evaluated in patients with advanced coronary disease who could not be optimally managed using conventional medical therapy or standard revascularization procedures. In this population, rFGF-2 administered as an IC infusion was well tolerated over a 100-fold dose range (0.33 μg/kg to 36 μg/kg). Hypotension was dose-related and dose limiting; in all cases, it was manageable by administration of IV fluids. The MTD was 36 μg/kg. Laboratory safety parameters and retinal examinations demonstrated mild and mainly transient changes.

Serious adverse events were common but did not appear to be dose related. Four deaths and four major cardiac events occurred but did not appear to be related to dose or time of administration. Preliminary efficacy data suggested improvement in the patients’ quality of life as assessed by SAQ, and in exercise tolerance measured by treadmill exercise testing.

In addition to these relatively subjective endpoints in this open-label study, there was objective evidence of increased regional wall motion and improved myocardial perfusion in
the most ischemic areas of the heart at all time points compared with baseline.

SAFETY AND TOLERABILITY OF RFGF-2 ADMINISTRATION. The ability to administer fairly high doses of rFGF-2 (up to 36 μg/kg IC) without significant hemodynamic effects is somewhat surprising given prior reports of severe FGF-2-induced hypotension (11) and the known capacity of this cytokine to stimulate NO release and induce arteriolar vasodilation (33). Hypotension was dose-related and dose limiting, but was rapidly correctable by IV fluids. This finding is in sharp contrast to clinical experience with another NO-releasing growth factor, VEGF-A165, where profound hypotension limits systemic administration (34). This difference in part may be attributable to careful hemodynamic monitoring in these patients and a requirement for adequate filling pressure (>12 mm Hg) before initiation of rFGF-2 infusion.

Preclinical studies as well as limited clinical experience to date suggested that renal insufficiency due to membranous nephropathy accompanied by proteinuria (35) may be the most significant long-term side effect of FGF-2 administration. In this small trial, only four instances of proteinuria were observed. It should be noted, however, that all patients studied had normal renal function at baseline.

Four patients died during follow-up (8% mortality). Two deaths were sudden, one death was due to complications of cardiac transplantation and one death was due to complications of large-cell lymphoma. Both instances of sudden death occurred in patients with reduced left ventricular function (22% and 30%). Although sudden death may be part of the natural history of their disease, potential partial revascularization in these patients may have induced ventricular tachyarrhythmias. The diagnosis of large-cell non-Hodgkin’s lymphoma 10 days after rFGF-2 infusion most likely reflected the presence of disease that antedated IC rFGF-2 administration. Nevertheless, it is possible that rFGF-2 may have exacerbated the lymphoma course (36).

Additional serious side effects included the occurrence of non-Q-wave myocardial infarction in four patients, raising the possibility that FGF-2 may have promoted growth, or destabilization of coronary plaque (37,38) owing to its broad-spectrum mitogenicity and chemotactic activity. The latter possibility may be particularly relevant given the ability of FGFs to induce angiogenesis in vasa vasorum (37–39) and the association between plaque angiogenesis and its growth (40,41) and stability (42). Although these concerns are certainly worrisome, in the absence of a control group causal relationships cannot be confirmed or discounted.

PRELIMINARY EFFICACY OF RFGF-2 THERAPY. Although the small sample size and the absence of a control group preclude any definitive conclusions regarding efficacy, several findings suggest potential clinical benefits of intracoronary rFGF-2 administration. In particular, quality of life, as assessed by the SAQ, improved in treated patients at day 57 compared with baseline, and this improvement was sustained for six months. The magnitude of improvements in the five SAQ scales was similar to that seen following PTCA and CABG in patients with ischemic heart disease (29,30). There was also a significant improvement in exercise capacity, as measured by exercise treadmill testing, seen at days 57 and 180. Of note, there was minimal improvement at day 29. The late occurrence of improvement in exercise testing is in keeping with the assumed time course of coronary angiogenesis. However, the absence of a dose response tempers the preliminary efficacy seen in this study.

In addition to these subjective measures of clinical status, resting MR imaging was performed to assess left ventricular function and myocardial perfusion. Using this approach we detected no difference in overall left ventricular ejection fraction at any time during the study. However, there was a significant improvement in systolic thickening of the target wall at day 29, which was maintained at six months, and was paralleled by a significant reduction in the size of the ischemic myocardium as assessed by blood arrival imaging. Although cardiac MR imaging is considered the “gold standard” for evaluation of left ventricular function (43,44), its application to clinical trials in coronary disease is very limited (45). Similarly, despite recent advances in MR-based perfusion assessment of the myocardium (31,32,46), there has been no substantial clinical experience with this imaging modality (47). In prior animal studies we have documented improvement in MR-assessed parameters of left ventricular function in the setting of angiogenic growth factor therapy (9,48). In addition, the newly developed variation of MR perfusion imaging that relies on generation of space-time maps proved capable of detecting changes in coronary perfusion in a pig ameroid model (31) and proved capable of detecting improved regional myocardial perfusion in patients treated with epicardially administered sustained release FGF-2 (49).

Clinical trials of coronary angiogenesis. It is important to consider the result of this trial in light of other recently reported trials of therapeutic coronary angiogenesis. The phase I open-label study of intracoronary (n = 15) and intravenous (n = 28) VEGF165 reported improvements in both angina class and exercise performance. However, a larger double-blind study of a single intracoronary infusion of VEGF165 followed by three intravenous infusions over seven days, failed to demonstrate any improvement in symptoms, exercise testing or nuclear perfusion imaging at day 60 compared with placebo controls (34). These results underscore the unreliability of an open-label study design to assess efficacy and an unusually large and long-lasting placebo effect in this patient population. We have reported a randomized, double-blind, placebo-controlled trial of sustained release FGF-2 administered perivascularly in conjunction with CABG that demonstrated improved myocardial perfusion in territories treated with 100 μg FGF-2 but not 10 μg FGF-2 or placebo (49).

A fundamental question pertaining to IIC delivery is how
a drug with a relatively short plasma half-life can promote a relatively long-term process such as new collateral formation. One possible explanation is that first-pass extraction at the desired site of action is the primary determinant of FGF-2 biological effect. Although such extraction certainly occurs, animal studies demonstrated that <1% of $^{125}$I-FGF-2 administered using the intracoronary route is deposited in the myocardium at 1 h and much less remains at 24 h (50). Although there is enhanced first-pass FGF-2 uptake in ischemic compared with normal myocardium (50), presumably due to increased expression of cellular heparan sulfates and FGF receptor-1 (51), myocardial levels fall to very low levels at 24 h in both normal and ischemic regions of the heart (50). One speculative explanation is that this transient accumulation of FGF-2 in the ischemic myocardium sets in motion a self-amplifying cascade that includes the influx and endothelial adhesion of monocytes/macrophages (52) and stimulation of expression of VEGF and other angiogenic cytokines, which may lead to prolonged and sustained action (5).

Conclusions. This Phase I, open-label dose-escalation study of a single IC infusion of rFGF-2 in patients with severe ischemic heart disease supports the safety and tolerability of this mode of FGF-2 delivery. This was accompanied by an improvement in quality of life, exercise capacity, and regional left ventricular function, and a reduction in the extent of resting myocardial ischemia as assessed by MR imaging in this uncontrolled study. The efficacy and safety of IC rFGF-2 is currently being evaluated in a large Phase II, randomized, double-blind placebo-controlled trial (FIRST, FGF-2 Initiating Revascularization Support Trial).

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