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Randomized Trial of a GPIIb/IIIa Platelet Receptor Blocker in Refractory Unstable Angina

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Background Patients with unstable angina despite intensive medical therapy, ie, refractory angina, are at high risk for developing thrombotic complications: myocardial infarction or coronary occlusion during percutaneous transluminal coronary angioplasty (PTCA). Chimeric 7E3 (c7E3) Fab is an antibody fragment that blocks the platelet glycoprotein (GP) IIb/IIIa receptor and potently inhibits platelet aggregation.

Methods and Results To evaluate whether potent platelet inhibition could reduce these complications, 60 patients with dynamic ST-T changes and recurrent pain despite intensive medical therapy were randomized to c7E3 Fab or placebo. After initial angiography had demonstrated a culprit lesion suitable for PTCA, placebo or c7E3 Fab was administered as 0.25 mg/kg bolus injection followed by 10 μ g/min for 18 to 24 hours until 1 hour after completion of second angiography and PTCA. During study drug infusion, ischemia occurred in 9 c7E3 Fab and 16 placebo patients ($P=.06$). During hospital stay, 12 major events occurred in 7 placebo patients (23%), including 1 death, 4 infarcts, and 7 urgent interventions. In the

c7E3 Fab group, only 1 event (an infarct) occurred (3%, $P=.03$). Angiography showed improved TIMI flow in 4 placebo and 6 c7E3 Fab patients and worsening of flow in 3 placebo patients but in none of the c7E3 Fab patients. Quantitative analysis showed significant improvement of the lesion in the patients treated with c7E3 Fab, which was not observed in the placebo group, although the difference between the two treatment groups was not significant. Measurement of platelet function and bleeding time demonstrated >90% blockade of GPIIb/IIIa receptors, >90% reduction of ex vivo platelet aggregation to ADP, and a significantly prolonged bleeding time during c7E3 Fab infusion, without excess bleeding.

Conclusions Combined therapy with c7E3 Fab, heparin, and aspirin appears safe. These pilot study results support the concept that effective blockade of the platelet GPIIb/IIIa receptors can reduce myocardial infarction and facilitate PTCA in patients with refractory unstable angina. (*Circulation*. 1994;89:596-603.)

Key Words • angina • platelets • glycoproteins

The term "unstable angina" encompasses a range of clinical situations related to sudden worsening of preexisting coronary disease.^{1,2} The underlying pathophysiological mechanism is a dynamic process, thought to begin with rupture of an atherosclerotic plaque and ulceration of the plaque surface, leading to platelet aggregation and nonocclusive or occlusive thrombosis.³⁻⁵ In most patients, resolution of the thrombus and stabilization of the plaque will occur, and further ischemic symptoms can be prevented with bed rest and drugs that reduce myocardial oxygen consumption and prevent thrombosis.^{2,6,7} In a subgroup of patients, however, ischemic episodes continue despite intensive antianginal therapy, including nitrates, β -blocking agents, heparin, and aspirin.² Patients with such "refractory angina" are usually offered urgent percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG), even though these urgent procedures are associated with increased morbidity and

mortality in comparison with elective PTCA or CABG.⁸⁻¹⁰ This increased complication rate is thought to be associated with ongoing intracoronary thrombosis.¹¹

Removal of platelet aggregates and thrombus in patients with refractory angina may help to relieve acute ischemia and to reduce the risk of urgent PTCA. However, administration of thrombolytic drugs in patients with refractory unstable angina has not demonstrated any beneficial effect.¹²⁻¹⁶ This ineffectiveness may result in part from activation of platelets by these agents.

The chimeric 7E3 (c7E3) monoclonal antibody Fab fragment is a potent inhibitor of platelet aggregation. The antibody inhibits aggregation by blocking the glycoprotein (GP) IIb/IIIa receptor on the platelet surface, thereby blocking the final common pathway of platelet activation and aggregation.¹⁷⁻¹⁹ In a double-blind randomized placebo-controlled pilot study, the safety and preliminary efficacy of c7E3 Fab treatment were studied in patients with refractory unstable angina who were undergoing PTCA. It was hypothesized that c7E3 Fab in combination with nitrates, heparin, and aspirin would facilitate stabilization of the culprit coronary lesion and thus reduce recurrent ischemia during the waiting period for PTCA and reduce the complication rate during and after the PTCA procedure. The effect of c7E3 Fab on the severity of the culprit coronary lesion was assessed by quantitative angiographic analysis.

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Methods

Patient Selection

Patients between 21 and 75 years old who exhibited at least one episode of angina with concomitant dynamic ST-T segment changes were eligible for the study. In addition, at least one episode of ischemia (either chest pain or ST-T changes) had to occur despite bed rest and medical treatment with intravenous heparin and nitrates. Coronary angiography was performed within 24 hours after the most recent episode of ischemia. Those patients with a single culprit lesion suitable for PTCA were enrolled, provided that a second coronary angiogram, followed by PTCA, could be performed 18 to 24 hours after the first (diagnostic) angiogram. Patients were excluded if they exhibited features of ongoing ischemia requiring immediate intervention. Other exclusion criteria were prior PTCA of the same coronary segment within 6 months; a previous myocardial Q-wave infarction within 7 days; female sex with childbearing potential; recent major trauma including resuscitation, surgery, or gastrointestinal or genitourinary bleeding within the past 6 weeks; known hepatic or renal disorder; history of bleeding diathesis or a platelet count of $<100\,000/\text{mm}^3$; and known autoimmune disorders. Informed consent was obtained after completion of the diagnostic angiogram and before protocol-specific measures.

Medical Treatment

Patients were randomized to receive either c7E3 Fab or placebo in a double-blind manner. c7E3 Fab was administered as an intravenous bolus injection of 0.25 mg/kg, followed by a continuous infusion of 10 $\mu\text{g}/\text{min}$. Study medication was drawn through a 0.22- μm low-protein-binding filter and administered through an in-line 0.22- μm low-protein-binding filter, starting within 4 hours after completion of the first coronary angiogram. Infusion of the study drug was to continue until 1 hour after the completion of the PTCA procedure, which was scheduled between 18 and 24 hours after the start of the infusion. In patients with severe recurrent ischemia, the second angiogram and PTCA could be performed urgently, at the discretion of the investigator.

All patients were concomitantly treated with intravenous nitroglycerin at a dose between 50 and 200 $\mu\text{g}/\text{min}$, with heparin at a dose sufficient to achieve a prolongation of the activated partial thromboplastin time to 2.0 to 2.5 times the control value, and with aspirin at a minimum dose of 80 mg once a day. Patients who were not on aspirin treatment at the start of the study received an initial dose of 250 mg aspirin. Other medication, such as β -blockers and calcium channel blockers, were continued as before randomization and adjusted as required by the clinical status.

Coronary Angiography and Angioplasty

Coronary arteriography was performed by the Judkins technique. Heparin 2500 to 5000 IU was administered at the beginning of the procedure. Low-osmolar contrast medium was used for all angiograms. The coronary segment responsible for the ischemia (culprit lesion) was identified from the angiographic appearance, in combination with the location of the ECG changes during ischemia. At least two orthogonal projections were made of the culprit lesion, after intracoronary injection of 1 to 3 mg of isosorbide dinitrate. In addition, at least three projections of the left coronary artery and at least two projections of the right coronary artery were filmed. During the first and the second angiograms, the same projections and x-ray gantry setting were used. All coronary angiograms were centrally assessed by two observers who were blinded with respect to treatment assignment. The following items were visually scored: TIMI flow grade²⁰ of the culprit artery; presence of intracoronary thrombus, defined as an intraluminal filling defect visible during at least one complete cine run; and stenosis severity as visually assessed in multiple

projections. In addition, the culprit lesions were analyzed in a quantitative manner with the computer-based Cardiovascular Angiography Analysis System.²¹ Minimal lumen diameter was calculated with the catheter tip as a scaling device. The percent diameter stenosis was obtained by comparing the minimal diameter value at the obstruction site with the interpolated reference contour in the same position. The extent of the obstruction was determined from the diameter function on the basis of curvature analysis and expressed in millimeters. "Plaque area" is the difference in area in square millimeters between the reference and detected contours over the length of the lesion.²² Values from two orthogonal projections were averaged.²³

After the second angiogram, 10 000 IU heparin and 250 mg aspirin were administered before the angioplasty procedure. In case of a prolonged procedure, extra doses of 5000 IU heparin were administered every hour during the procedure. Primary success of angioplasty was defined as $<50\%$ residual diameter stenosis of the culprit vessel, without signs of myocardial infarction or ischemia and without urgent coronary bypass operation or death.

ECG Monitoring

A continuous three-lead vector ECG was recorded with a computerized system (MIDA-1000²⁴) from randomization until 4 hours after PTCA. The orthogonal leads (Frank lead system) as well as the derived 12-lead ECG were analyzed for ST-T segment changes by a central assessment committee without knowledge of the treatment. Reversible ST-T changes were classified as either ST segment elevation or depression of at least 0.1 mV, T-wave changes (development of negative or biphasic T waves or pseudonormalization of preexisting T-wave abnormalities), or minimal ST-T changes not fulfilling the criteria for the other categories. The MIDA-1000 system computed averaged ECG complexes during 2-minute intervals after exclusion of all abnormal beats (premature ventricular contractions, noise, etc). Thus, ECG changes were detected only if these persisted during at least one sample interval. Episodes of ischemia were scored in four categories: (1) pain with concomitant ECG changes, (2) pain without ECG changes, (3) pain without ECG recording available, and (4) ECG changes without pain (silent ischemia). ST-T segment changes at the time of angiography and PTCA were excluded from assessment.

Assessment of Bleeding and Laboratory Test

All patients underwent daily clinical assessment for bleeding complications and other adverse events. Bleeding events were defined as major or minor according to the Thrombosis in Myocardial Infarction (TIMI) Study Group criteria.²⁵ Major bleeds were defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin (Hb) $>3.1\text{ mmol}/\text{L}$ or with a hematocrit (Ht) decrease of at least 15%. Bleeding was defined as minor if (1) it was spontaneous gross hematuria or hematemesis; (2) blood loss was observed along with an Hb decrease $>1.9\text{ mmol}/\text{L}$ or an Ht decrease of at least 10%; or (3) no bleeding site was identified despite an effort to find one along with a decrease in Hb $>2.5\text{ mmol}/\text{L}$ or an Ht decrease of at least 12%. To account for transfusion, the change in Hb was calculated as the change in Ht/3 plus the number of units of blood transfused.²⁶

Laboratory evaluations for hematology and cardiac enzymes were performed during infusion and throughout the subsequent hospitalization. Bleeding time was measured at baseline and just before the second angiography. Three different methods for bleeding time were used between hospitals: Ivy (normal, 1 to 4 minutes), Simplate (normal, <8 minutes), or Duke (normal, 1 to 3 minutes). In a subgroup of 18 patients in one hospital, the platelet function was studied by measuring GPIIb/IIIa receptor blockade with an ex vivo radiometric method using ¹²⁵I-7E3 murine IgG antibody solution in Tris buffer, supplied by Centocor,¹⁸ and by assessment of ex vivo

platelet aggregation in response to ADP at final concentrations of 2, 5, and 20 $\mu\text{mol/L}$, respectively. Results are expressed as maximum percent aggregation achieved after 5 minutes in the test platelet-rich plasma, using platelet-poor plasma as a reference of 100%. Measurements of platelet function were made at baseline and 2 and 6 hours after the start of the study drug infusion, just before the second angiogram and after completion of PTCA, and 48 and 72 hours after the start of the infusion.

Because of the possibility of antibody formation against c7E3 Fab, serum was sampled for human antichimeric antibodies (HACA) at baseline, before and after PTCA, before discharge, and again after 2, 6, and 12 weeks. Measurements of HACA titers were performed in a central laboratory. An enzyme immunoassay was used in which patient sera were incubated with biotinylated c7E3 Fab that was bound to microtiter plates via a streptavidin linkage. The presence of HACA was measured in a standard colorimetric assay system using horseradish peroxidase-conjugated goat antihuman Fc and reading the resultant optical density spectrophotometrically. An assessment of positive immune response to c7E3 Fab was based on the magnitude and specificity of assay results from postinjection samples relative to the preinjection sample.¹⁹

Study End Points

The efficacy end points were defined as death, myocardial infarction (as defined by creatine kinase greater than two times the upper limit of normal), and recurrent ischemia (both symptomatic and silent ischemia). Before data analysis, it was decided to use a composite primary end point for statistical analysis, including death, myocardial infarction, and recurrent ischemia requiring urgent intervention (specifically, PTCA, CABG, intra-aortic balloon pump, or stent implantation to maintain coronary patency). The occurrence of all end points was validated by a central clinical end point committee. Secondary efficacy analyses included the occurrence of all recurrent ischemic episodes (as described in the previous section) and angiographic end points. Angiographic end points included both qualitative visual assessment of changes and quantitative differences between the first and second coronary angiograms.

Statistical Analysis

Differences between groups were analyzed on an "intention-to-treat" basis, with a two-tailed Student's *t* test for continuous variables or Fisher's exact test for categorical variables. Changes in quantitatively measured coronary artery stenosis, as well as in bleeding time in each group, were compared with a two-tailed paired *t* test, and differences between groups were tested with unpaired *t* tests. Differences in the total numbers of ischemic episodes were examined with the Mann-Whitney rank sum test.

Results

Between September 1991 and July 1992, 60 patients were enrolled in the study. Thirty patients received c7E3 Fab, and 30 patients received placebo. Patient enrollment was slow because many physicians appeared to be reluctant to postpone PTCA for 24 hours after the first angiogram. Most baseline characteristics were similar between the groups (Table 1), but the patients in the placebo group had a longer history of angina ($P=\text{NS}$) and more extensive coronary artery disease ($P<.05$). The distributions of the ischemia-related vessels were similar in both groups. In the c7E3 Fab group, 22 of 30 patients (73%) had their first angiogram within 12 hours after the most recent episode of ischemia; in the placebo group, 26 patients (87%). Medication at the time of the most recent episode of ischemia was inten-

TABLE 1. Clinical, Medical, and Angiographic Characteristics at Baseline

	c7E3 Fab (n=30)	Placebo (n=30)
Male, n	20	24
Age, y (median, range)	61, 38-73	60, 38-73
History of		
Myocardial infarction within 7 days	6	5
Angina for more than 4 weeks	8	14
PTCA	4	5
CABG	...	2
Medication before ischemia		
Heparin	26	27
Aspirin	21	23
Nitrates		
Intravenous	24	27
Oral	4	2
β -Blocker	22	24
Calcium channel blocker	15	22
ECG changes during ischemia		
ST elevation	8	13
ST depression	11	8
ΔT	9	5
Other*	2	4
Ischemia-related vessel		
Left anterior descending artery	16	14
Right coronary artery	6	10
Left circumflex artery	8	6
Multivessel disease	6	15

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery.

*The ECGs before enrollment showed minimal (2 placebo and 1 c7E3 Fab) or no changes (1 placebo patient) or were not available for review by the committee (1 patient in each group). The difference between the incidence of multivessel disease between the two groups was statistically significant ($P<.05$).

sive and similar in both groups (Table 1). During the study drug infusion, all patients received intravenous nitrates and heparin, and all but two (one in each group) received aspirin. The ECG changes during ischemia before enrollment were also similar.

Recurrent Ischemia

During infusion of the study drug, ischemia occurred in 9 patients treated with c7E3 Fab and in 16 placebo patients ($P=.06$), whereas 9 and 6 patients, respectively, developed ischemia after PTCA (Table 2). Most patients had multiple episodes of ischemia. The total number of patients with different types of ischemia was not different between the two treatment groups ($P=.15$). Similarly, the total number of episodes was not significantly different between patients receiving c7E3 Fab (33 episodes) or placebo (56 episodes, $P=.17$).

In 1 placebo patient, an urgent intervention was performed because of recurrent ischemia before the

TABLE 2. Recurrent Ischemia

	c7E3 Fab		Placebo	
	A	B	A	B
n	30		30	
Pain+ST-T changes	2	...	5	3
Pain-ST-T changes	1	...	2	...
Pain, no ECG	1	1
Silent ST-T changes	5	8	12	5
Patients with pain or ST-T changes	9	9	16	6
Total No. of patients	13		18	

Patients with recurrent ischemia between diagnostic and second angiography (A) or after percutaneous transluminal coronary angiography (PTCA) until discharge (B). Multiple episodes and different types of ischemia could occur in one patient. Episodes of ischemia during angiography or PTCA were not included.

scheduled PTCA. During the hospital stay, a total of 12 major events, defined as death (n=1), myocardial infarction (n=4), or urgent intervention because of severe recurrent ischemia (n=7), occurred in 7 placebo patients, and 1 event (a myocardial infarction) occurred in a patient treated with c7E3 Fab (Table 3; 1 versus 7 patients, *P*=.03). Three placebo patients experienced more than 1 major event.

Multivessel disease was present in 5 of the 7 placebo patients who developed an event, whereas an event occurred in a c7E3 Fab-treated patient with single-vessel disease. After correction for the imbalance in baseline characteristics, the difference between the two groups was not statistically significant in this pilot study (*P*=.16).

Qualitative and Quantitative Angiographic Data

The TIMI flow grades of the culprit artery on the diagnostic angiogram were comparable between the two

groups (Table 4). After treatment, the flow was improved in six patients in the c7E3 Fab group. In the placebo group, flow improved in four and worsened in three patients. Although slightly more thrombi were seen in the c7E3 Fab group at baseline, the number of thrombi was reduced by the same number in both groups.

Quantitative analysis of the ischemia-related segment did not reveal any changes during the study period in the placebo group (Table 4). Conversely, between the first and second angiograms, an increase in minimal luminal diameter and significant reductions in the percent diameter stenosis, plaque area, and stenosis length were observed in the c7E3 Fab-treated patients. Nevertheless, direct comparison of the changes between the two treatment groups failed to reach statistical significance, which may be because of the sample size in this pilot study.

TABLE 3. Major Events

	c7E3 Fab		Placebo	
	A	B	A	B
n	30		30	
Death	1*
Myocardial infarction	...	1	3*†	1
Urgent PTCA	1*	2*‡
Urgent CABG	3†‡
Stent	1	...
Patients with event, period A or B	...	1	4	5
Total patients with event per treatment group	1		§	7

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery. Patients with events during study drug infusion including second angiography and PTCA (A) or after discontinuation of study drug until discharge (B).

One major event occurred in 1 c7E3 Fab patient 3 days after PTCA, whereas 12 events occurred in 7 placebo patients. In the placebo group, 3 patients had multiple events.

*A 61-year-old man died after a complicated clinical course, including two urgent PTCA procedures because of severe recurrent ischemia and myocardial infarction. Heart failure and hypotension were treated with an intra-aortic balloon pump and mechanical ventilation. Severe bleeding occurred at puncture sites and gastric and pulmonary sites, for which a total of 17 IU transfusions were given. Finally, *Pseudomonas* sepsis and multiple organ failure resulted in death 26 days after allocation.

†Another patient developed myocardial infarction during PTCA followed by persistent pain, necessitating urgent CABG.

‡The third patient developed recurrent ischemia after an initially successful PTCA of the right coronary artery and underwent repeat PTCA followed by urgent CABG.

§*P*=.03.

TABLE 4. Angiographic Results (Visual Assessment)

	c7E3 Fab (n=30)		Placebo (n=30)		
	I	II	I	II	
Qualitative analysis					
TIMI flow					
0	1	1	4	3	
1	2	1	...	2	
2	10	5	7	6	
3	17	23	19	20	
Improved		6		4	
Worsened		...		3	
Thrombus present	6	3	3	1	
Quantitative analysis					
Diameter stenosis, %	66±9	*	62±10	66±19	65±16
Obstruction diameter, mm	0.92±0.29		0.97±0.30	0.87±0.43	0.89±0.39
Extent of obstruction, mm	7.3±2.2	*	6.9±2.1	7.2±3.4	7.3±2.9
Plaque area, mm ²	8.2±3.4	*	7.1±2.5	9.1±6.8	8.5±4.0

No. of patients with different aspects of the culprit lesion before (I, first, diagnostic angiogram) or during (II, second, pre-PTCA angiogram) administration of c7E3 Fab or placebo. The quantitative analysis is presented as mean±SD of the measurements.

* $P < .05$ for paired comparison of angiogram I vs II in each patient group. The changes between patient groups (c7E3 Fab vs placebo) did not reach statistical significance.

Angioplasty Procedure

Angioplasty was performed in all 60 patients. In 1 patient who received c7E3 Fab, PTCA was delayed because of a total occlusion with a large intracoronary clot at the second angiogram. He was treated with alteplase 50 mg intracoronary infused over 30 minutes, followed by 50 mg intravenously over 2 hours. The next day, the clots were partly resolved, and PTCA was performed successfully. One other c7E3 Fab patient with a thrombocytosis of unknown origin received alteplase during PTCA because of persistent thrombus formation. PTCA was completed with success, and the subsequent clinical course was uncomplicated. The total success rate of the angioplasty procedure was 83% in the c7E3 Fab group and 70% in the placebo group.

Platelet Function and Bleeding Time

Platelet function, as measured by the number of free GPIIb/IIIa binding sites per platelet and as ex vivo ADP-induced platelet aggregation, was studied in 18 patients, 9 in each group. The number of free receptor binding sites hardly changed during placebo infusion, whereas soon after the start of c7E3 Fab infusion, the median number of free binding sites decreased to 7% of the baseline value (Figure). Approximately 48 hours after the end of the infusion ($t=72$ hours), this number had returned to 61% of the baseline value. Platelet aggregation showed a similar inhibition of platelet function after c7E3 Fab infusion. Two hours after the start of the infusion, aggregation in response to 2, 5, and 20 μmol ADP was reduced to 0%, 0%, and 17% of the baseline value, respectively, and was returned to 61%, 66%, and 77% approximately 48 hours after the end of the infusion. In the subset of patients in whom these measurements were obtained, no relation was observed

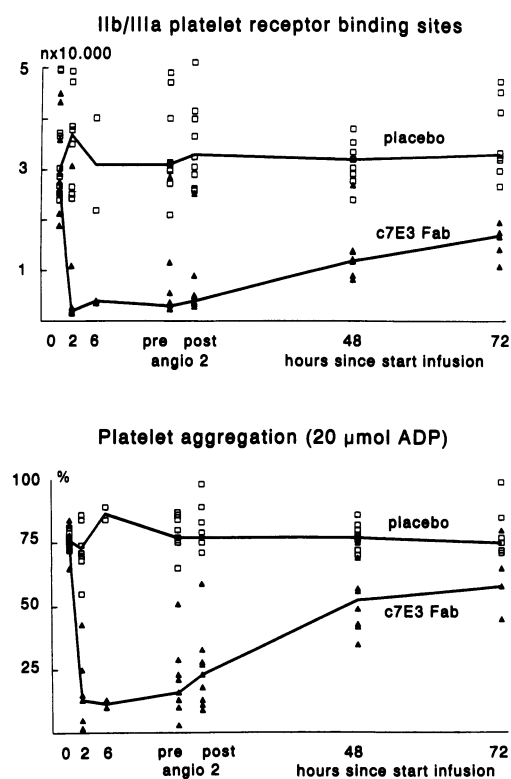
between the level of platelet inhibition and either recurrent ischemia or bleeding complications. One patient who was treated with c7E3 Fab did not show a significant inhibition of the platelet function (Figure). Soon after the start of the study infusion, thrombocytosis was discovered in this patient, with platelet counts of 957 000/mm³.

Bleeding times were measured by different methods (Ivy, Simplate, and Duke). Seven patients had a prolonged bleeding time at baseline, which could be explained by measurement after start of the infusion in two patients and concomitant aspirin use in the others. A prolongation of bleeding time exceeding twice the baseline value was observed in 18 of 23 patients during infusion with c7E3 Fab and in only 3 of 27 placebo patients ($P < .001$).

Complications

There were no bleeding events requiring surgical intervention. Five patients received blood transfusions, three in the c7E3 Fab group and two in the placebo group. According to the TIMI criteria, major bleeding occurred in one patient after treatment with c7E3 Fab and in three patients after placebo treatment. Minor bleeding was observed in one placebo patient but not in the c7E3 Fab patients.²⁵ Thrombocytopenia did not occur in any patient receiving c7E3 Fab. In one placebo patient, thrombocytopenia developed (nadir, 12 000/ μL). This finding might be related to heparin therapy, since this was the only medication given that can induce thrombocytopenia, although such deep thrombocytopenia is a rare finding during heparin therapy.

Posttreatment serum samples for the determination of HACA responses were obtained in 29 of 30 c7E3 Fab-treated patients and in all placebo patients. The



Graphs showing platelet glycoprotein (GP) IIb/IIIa receptor blockade (top) and ex vivo platelet aggregation to 20 μ mol ADP (bottom). Values are given as median number and individual spread of free GPIIb/IIIa receptor binding sites and percentage of aggregation. \square indicates placebo patients; \blacktriangle , patients receiving c7E3 Fab. Note one c7E3 patient with number of binding sites similar to placebo. This particular patient had thrombocytosis.

pretreatment optical density measurements varied between 0 and 1.5 ($n=56$). One patient who received c7E3 Fab had a HACA response specific for the murine variable region of c7E3 Fab, exceeding the pretreatment range. Optical density values were 2.1 at 2 weeks and 2.6 at 12 weeks.

Discussion

Current treatment of patients with unstable angina includes drugs that reduce myocardial oxygen demand,⁶ as well as aspirin and heparin.^{7,27} In patients with recurrent episodes of ischemia despite intense combination therapy, intracoronary thrombosis is frequently observed, particularly if angiography is performed early after the most recent ischemic episode.^{28,29} In such patients, a more potent inhibitor of platelet aggregation, such as a blocker of the platelet GPIIb/IIIa receptor, may facilitate lysis of the thrombus and prevent rethrombosis at the site of plaque rupture, thus averting future ischemic episodes.

The present pilot study supports the concept that treatment with c7E3 Fab in patients with refractory unstable angina does reduce recurrent ischemic episodes and facilitates PTCA. In 30 patients treated with placebo, 7 (23%) had a total of 12 events. In contrast, only 1 of the 30 patients treated with c7E3 Fab had a single event (3%, $P=.03$). Recurrent ischemia during the 18 to 24 hours of treatment before PTCA was reduced by 44% ($P=.06$) in patients receiving c7E3 Fab,

and the severity of the culprit lesion was improved (Table 4). The proportion of patients with major events, as specified in Table 3, in the placebo group was 23%, which is comparable to the incidence of 36% in a previous study with similar design.¹² Urgent PTCA in such patients has been associated with a 10% to 15% complication rate.^{11,12} A similarly high complication rate (30%) was observed in the present placebo group.

This study was randomized and conducted in a double-blind manner. Nevertheless, the results are not conclusive, because the number of patients in this pilot study is small and because an imbalance of baseline characteristics existed in favor of the c7E3 Fab-treated patients. In particular, the presence of multivessel disease was more frequent ($P<.05$), and more patients had previous angina ($P=NS$) in the placebo group. Furthermore, it cannot be excluded that the investigators became aware of the actual treatment in some patients because of prolonged bleeding times measured during c7E3 Fab therapy. However, final assessment of events, ECG recordings, and angiograms was done centrally, without knowledge of treatment assignment.

Other Patient Studies With 7E3 Antibodies

Open-label nonrandomized studies with murine (m) 7E3 F(ab')₂ and 7E3 Fab also suggest that such treatment may be beneficial in patients with acute coronary syndromes. After single bolus doses of m7E3 F(ab')₂ in patients with unstable angina, anginal pain did not occur within the first few hours while the bleeding time was still prolonged (>10 minutes) but returned in several patients when the bleeding time was normalized.¹⁸ More recently, Kleiman et al³⁰ reported better coronary artery patency and a trend for fewer ischemic events after treatment with m7E3 Fab after thrombolysis, in combination with heparin and aspirin treatment, compared with a group of patients with acute myocardial infarction who did not receive m7E3 Fab. As in the present study, administration of the antibody was well tolerated and was not associated with a higher bleeding risk.

In a recently presented trial of 2100 patients undergoing "high-risk" angiography, a single bolus of c7E3 Fab did not prevent recurrent ischemic events.³¹ In that trial, a marked reduction of events was reported during and after a bolus injection followed by 12 hours of infusion of c7E3 Fab at the same dosage as in the present pilot study. In the present study, c7E3 Fab was administered during at least 18 hours before PTCA. One hour after PTCA, the drug was discontinued to allow sheath removal. These two studies indicate that prolonged (≥ 12 hours) inhibition of platelet aggregation either before or after³¹ PTCA will be necessary to prevent ischemic events in patients with unstable coronary plaque. Additional studies are required to assess the optimal timing and duration of therapy with c7E3 Fab.

Degree of Platelet Function Inhibition and Safety

Extensive blockade of platelet GPIIb/IIIa receptors and inhibition of ex vivo platelet aggregation were demonstrated in the subgroup of c7E3 Fab-treated patients for whom this was measured. During the infusion of c7E3 Fab, approximately 90% of the platelet GPIIb/IIIa receptors were blocked, resulting in nearly complete inhibition of platelet function, as measured by

ADP-induced platelet aggregation and a markedly prolonged bleeding time. Reversibility of the inhibition was illustrated by partial recovery of platelet function within 48 hours after the end of the infusion ($t=72$ hours, Figure). These data are in agreement with previous open-label studies with m7E3 F(ab')₂ and m7E3 Fab,^{18,32} demonstrating that c7E3 Fab produced a potent, yet reversible, inhibition of platelet function in patients with unstable angina who are treated concomitantly with heparin and aspirin. Nevertheless, administration of c7E3 Fab was well tolerated in all patients, and no serious, severe, or life-threatening adverse events were observed. There was no difference in the incidence of major or minor bleeding events between placebo-treated and c7E3 Fab-treated patients; in fact, three placebo-treated patients had major bleeding events by TIMI criteria,²⁵ compared with only one c7E3 Fab-treated patient. Therefore, infusion of c7E3 Fab up to 24 hours before and during PTCA appeared safe in patients receiving concomitant intravenous heparin and aspirin.

No thrombocytopenia was observed in any patients receiving c7E3 Fab in this study. Severe thrombocytopenia was reported in a few patients injected with m7E3 Fab.³⁰ Unfortunately, it remains uncertain whether this was a true adverse drug effect or an artifact (so-called pseudothrombocytopenia in vitro). Nevertheless, it is reassuring that this problem did not recur after modification of the administration procedure, including the use of an in-line microfilter.

In the present study, as well as other c7E3 Fab studies,³² some patients demonstrated high pretreatment reactivity in the HACA assay, yet demonstrated platelet GPIIb/IIIa receptor blockade and inhibition of platelet aggregation in response to c7E3 Fab that was no different from that observed in patients with low pretreatment reactivity. The high pretreatment reactivity was also not associated with adverse events (eg, thrombocytopenia or allergic reactions) after c7E3 Fab injection. Only one patient exhibited posttreatment reactivity that was greater than the observed pretreatment range of responses. This finding of apparently low immunogenicity with the humanized antibody fragment is consistent with other trials of c7E3 Fab.³² The collective investigational experience with c7E3 indicates that this agent has substantially less immunogenic potential than the m7E3 Fab agent; studies with m7E3 Fab have reported human anti-murine antibody rates as high as 50%.³⁰ Nevertheless, the significance of both pretreatment and posttreatment assay reactivities observed in this study requires further investigation, particularly with respect to the safety of repeated c7E3 Fab dosing.

Conclusions

This pilot study is the first randomized, placebo-controlled study with c7E3 Fab in patients with refractory unstable angina pectoris. Despite intensive concomitant therapy with intravenous heparin, aspirin, and c7E3 Fab or placebo, no excess bleeding complications were observed. Overall, patients treated with c7E3 Fab had a more favorable course, with less recurrent ischemia, some resolution of coronary stenosis, and fewer complications compared with the placebo group. However, the series is small, and definitive assessment of the value of c7E3 Fab must await the completion of ongoing

larger trials. Still, these data indicate that potent inhibition of platelet aggregation may be of particular clinical value in patients with refractory unstable angina who undergo PTCA.

Appendix

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