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Antiplatelet therapy in therapy-resistant unstable angina

A pilot study with REO PRO (c7E3)

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Patients with unstable angina, refractory to intensive medical therapy, are at high risk of developing thrombotic complications, such as myocardial infarction and coronary occlusion during coronary angioplasty. As platelet aggregation and thrombus formation play an important role in this ongoing ischaemic process, a monoclonal platelet GPIIb/IIIa receptor antibody (c7E3) has been designed to modify the clinical course and underlying coronary lesion morphology.

To evaluate whether c7E3 could influence the incidence of complications, we randomized 60 patients to c7E3 or placebo after initial angiography had demonstrated a culprit lesion amenable for angioplasty. All patients exhibited dynamic ECG changes and recurrent pain attacks, despite intensive medical therapy. After study drug bolus and infusion, angiography was repeated and angioplasty performed.

Recurrent ischaemia during study drug infusion occurred in nine and 16 patients from the c7E3 and placebo groups, respectively ($P = 0.06$). Major events defined as death, myocardial infarction or urgent intervention occurred in one and seven patients, respectively ($P = 0.03$). One patient from the placebo group died as a result of recurrent infarction. Resolution of clots was only observed in the c7E3 group, combined with improvement in TIMI flow grade in 20% of patients. Quantitative angiography showed an improvement in percentage diameter stenosis in the c7E3 group, which was not observed in the placebo group, although the difference between the two treatment groups was not significant. No excess bleeding was observed in the treatment group. Thus, c7E3 bolus and infusion, combined with heparin and aspirin improved the clinical course, the coronary lesion morphology and rheology in patients with unstable angina, refractory to medical treatment.

Introduction

In 1989 Braunwald provided a classification for patients with unstable angina, based on the clinical circumstances under which the syndrome occurred and the severity of the symptoms[1]. A further subdivision took the intensity of medical treatment and the presence or absence of reversible electrocardiographic changes during anginal attacks into consideration. Outcome of patients with unstable angina could be predicted using this classification[2].

The underlying cause of unstable angina is thought to be rupture and ulceration of a preexistent atherosclerotic plaque, leading to platelet adhesion and aggregation, and thrombus formation[3]. In most patients the syndrome can be stabilized with bed rest and anti-ischaemic and antithrombotic therapy[4]. However, in a minority of patients ischaemic symptoms continue in spite of intensive medical therapy. Such patients with unstable angina refractory to medical treatment are usually referred for urgent angioplasty or bypass operation[2], even though interventions are associated with a higher complication rate compared with stable or stabilized unstable angina patients[5,6]. Prevention and or resolution of platelet aggregates and thrombi may help to prevent ongoing ischaemic attacks as well as angioplasty complications.

The value of thrombolytic therapy in evolving myocardial infarction has been established. It opens occluded coronary arteries, improves left ventricular function and reduces mortality by limiting infarct size[7,8]. Recent randomized trials in patients with unstable angina demonstrated angiographic improvement after thrombolytic therapy by opening occluded coronary arteries and reducing the incidence of intracoronary thrombi; however, this did not reduce in-hospital cardiac events[9,10]. This apparent discrepancy may be due to activation of platelet aggregation by thrombolytic drugs in patients with unstable angina. Thus, inhibition of platelet aggregation in these patients might be a better therapeutic option.

The chimeric 7E3 (c7E3) monoclonal antibody Fab fragment is a potent inhibitor of platelet aggregation. It blocks the glycoprotein IIb/IIIa fibrinogen receptor on the platelet surface, and by preventing the binding of fibrinogen to the platelet surface, platelet aggregation and platelet thrombus formation are inhibited[11].

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 undergoing percutaneous coronary angioplasty

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(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 ischaemia prior to 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 qualitative and quantitative angiographic analysis.

Patients and methods

PATIENT SELECTION

Patients were included in the study if they were between 21 and 75 years old and exhibited at least one episode of angina pectoris with concomitant dynamic ST-T segment changes. In addition, at least one episode of ischaemia (either chest pain or ST-T segment changes) had to occur despite bed rest, and medical treatment comprising at a minimum heparin i.v. and nitroglycerin i.v. Diagnostic coronary arteriography was performed within 12 h of the most recent episode of coronary ischaemia. Patients could be included, after informed consent had been obtained, if the diagnostic arteriogram showed a single culprit lesion amenable for PTCA. Total occlusion of the culprit vessel was considered acceptable for angioplasty if recent occlusion was suspected by the presence of intracoronary thrombi or contrast staining at the obstruction site. Patients were excluded if they exhibited features of ongoing ischaemia which required immediate intervention, had had PTCA of the same coronary segment less than 6 months before, had experienced recent major trauma including resuscitation, gastrointestinal or urinary tract bleeding less than 3 months before, had had persistent hypertension, known bleeding disorders, prior Q wave myocardial infarction less than 7 days before, or a platelet count of less than 100 000.mm^{-3}.

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^{-1}, followed by a continuous infusion of 10 μg.min^{-1}, starting within 4 h after completion of the first coronary angiogram.

Infusion of the study drug was to continue for 1 h after the completion of the PTCA procedure. Patients receiving placebo were administered a bolus of human serum albumin, followed by continuous infusion, and PTCA was scheduled between 18 and 24 h after the start of the infusion. In patients with severe recurrent ischaemia, 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 μg.min^{-1}, with heparin at a dose sufficient to achieve 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 and adjusted as required by the clinical status.

CORONARY ARTERIOGRAPHY AND ANGIOPLASTY

Coronary arteriography and left ventricular angiography were performed as soon as possible after the qualifying anginal attack using the Judkins technique. Heparin 2500 to 5000 IU was administered at the beginning of the procedure. A second angiogram was performed within 24 h after the start of study medication followed by angioplasty. The coronary artery responsible for the ischaemia was identified through lesion characteristics, electrocardiographic location of reversible ST-T segment changes and left ventricular wall contraction abnormalities. At least two orthogonal projections were made of the culprit coronary segment, after injection of 1–3 mg of isosorbide dinitrate. During the first and second angiogram, the same projections and X-ray gantry settings were employed to compare lesion severity. Low osmolar contrast medium (iopamidol) was used for all angiograms.

QUALITATIVE AND QUANTITATIVE ASSESSMENT OF CORONARY ANGIOGRAMS

All coronary and left ventricular angiograms were centrally assessed by two observers who were blinded to treatment assignment. The following items were visually scored after the first contrast injection: TIMI flow grade[12] of the culprit artery; stenosis severity, as visually assessed in multiple projections, and presence of intracoronary thrombus, defined as an intraluminal filling defect, visible during at least one complete cine-run, and surrounded on three sides by contrast medium[13]. A totally occluded coronary artery could contain a filling defect, but was not automatically scored as containing such a defect. In addition, all angiograms were analysed by the Core laboratory at Cardialysis, Rotterdam, NL, using the computer-assisted cardiovascular angiography analysis system[14,15]. Any area sized 6·9 × 6·9 mm in a selected cineframe (overall dimensions 18 × 24 mm) encompassing the desired arterial segment was digitized by a high-resolution CCD camera with a resolution of 512 × 512 pixels and 8 bits of gray level. Vessel contours were determined automatically, based on the weighted sum of the first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centreline directions of an arterial segment. A computer-derived estimation of the original arterial dimension at the site of the obstruction was used to define the interpolated reference diameter. This technique is based on a computer-derived estimation of the original diameter values over the analysed region (assuming there was no disease present) according to the diameter function. The absolute diameter of the stenosis as well as the reference diameter were measured, using the known guiding catheter diameter as a calibration factor. All contour positions of the catheter and arterial segments were corrected for pincushion distortion. 'Plaque area' is the difference in area in mm^2 between the reference and the detected contours over the length of the lesion[16].

EGG MONITORING

A continuous three-lead vector ECG was recorded from randomization until 4 h after PTCA with a computerized system (MIDA 1000)[17]. The orthogonal leads (Frank lead

system) as well as the derived 12-lead ECG were analysed 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 over 2-min intervals after exclusion of all abnormal beats (premature ventricular contractions, noise, etc). Thus, ECG changes were detected only if these persisted for at least one sample interval. Episodes of ischaemia were scored in four categories: (1) pain with concomitant ECG changes, (2) pain without ECG changes, (3) pain with no available ECG recording, and (4) ECG changes without pain (silent ischaemia). ST-T segment changes at the time of angiography and PTCA were excluded from assessment.

STUDY ENDPOINTS

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

STATISTICAL ANALYSIS

Differences between groups were analysed 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 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 ischaemic episodes were examined with the Mann-Whitney rank sum test.

Results

BASELINE CHARACTERISTICS

Between September 1991 and July 1992, 60 patients were enrolled in six different hospitals (see Appendix). Baseline characteristics are summarized in Table 1. The groups were balanced although more patients in the placebo group had sustained a previous infarct compared with the treatment group (P = ns), and more patients in the placebo group demonstrated multivessel disease, defined as a more than 50% diameter stenosis in one of the three main epicardial vessels. Medication at the time of the qualifying ischaemic attack was intense and similar in both groups.

Table 1 Baseline clinical, electrocardiographic and angiographic characteristics of patient groups

Group	c7E3Fab	Placebo
Male/female, n	20/10	24/6
Age (years), (median, range)	61, 38–73	60, 38–73
Previous infarct	9	16
within 7 days	6	5
Previous CABG	0	2
Previous PTCA	4	5
Medication prior to qualifying ischaemic attack		
Heparin	26	27
Asprin	21	23
Nitrates		
*intravenous	24	27
*oral	4	2
β-blocker	22	24
Calcium channel blocker	15	22
Ischaemia-related vessel		
Left anterior descending artery	16	14
Left circumflex artery	8	6
Right coronary artery	6	10
Multivessel disease	6*	15*

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; *$P = < 0{\cdot}05$.

RECURRENT ISCHAEMIA

During infusion of the study drug, ischaemia occurred in nine patients treated with c7E3 Fab and in 16 placebo patients ($P = 0.06$), whereas nine and six patients, respectively, developed ischaemia after PTCA (Table 2). Most patients had multiple episodes of ischaemia. The total number of patients with different types of ischaemia did not differ between the two treatment groups ($P = 0.15$), and the total number of episodes was not significantly different between patients receiving c7E3 Fab (33 episodes) or placebo (56 episodes, $P = 0.17$). In one placebo patient, an urgent intervention was performed because of recurrent ischaemia before the scheduled PTCA.

While in hospital, a total of 12 major ischaemic events occurred in seven placebo patients: death (n = 1), myocardial infarction (n = 4), urgent intervention because of severe recurrent ischaemia (n = 7). One event (a myocardial infarction) occurred in a patient treated with c7E3 Fab (Table 3; 1 vs 7 patients, $P = 0.03$). Three placebo patients experienced more than one major event. Multivessel dis-

Table 2 Recurrent ischaemia

	c7E3 Fab	Placebo
n	30	30
Pain + ST-T changes	2	5
Pain − ST-T changes	1	2
Pain, no ECG available	1	0
Silent ST-T changes	5	12
Patients with pain or ST-T changes	9	16

Patients with recurrent ischaemia between diagnostic and second angiography. Multiple episodes and different types of ischaemia could occur in one patient. Episodes of ischaemia during angiography or PTCA were not included.

Table 3 Major events

	c7E3 Fab (n = 30)	Placebo (n = 30)
Death	0	1
Myocardial infarction	1	4
Before PTCA	0	1
After PTCA	1	3
Urgent procedure	0	7
PTCA	0	3
CABG	0	3
Stent	0	1
Total events	1	12
Total number of patients with one or more major events	1	7

CABG = coronary artery bypass grafting.
PTCA = percutaneous transluminal coronary angioplasty.

ease was present in five of the seven placebo patients who developed an event, whereas the c7E3 Fab-treated patient with an event had 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 ($P = 0.16$). One patient from the placebo group died 26 days after allocation after a complicated clinical course, including two urgent PTCA procedures, myocardial infarction, heart failure, intra-aortic balloon pump and severe bleeding.

QUALITATIVE EVALUATION OF CORONARY ANGIOGRAMS

TIMI flow grade 3 in culprit arteries, assessed centrally by the Core Laboratory, was present in 57% and 63% of patients at the first angiogram in the placebo and treatment groups, respectively. A substantial improvement in coronary blood flow occurred after treatment in the c7E3 Fab patient group. In the placebo group, a mix of either improvement or deterioration was observed in TIMI flow score (Table 4).

Extensive filling defects in the coronary arteries were rare. Most filling defects were small, although visible in more than one projection and located distally from the culprit lesion. The number of intracoronary clots, and total occlusions, in the pre- and post-treatment angiogram are presented in Fig. 1. In the placebo group, one new occlusion was observed, in two cases patency was restored to totally occluded vessels, and in one of these two cases there were

Table 4 Qualitative angiographic data

Group	c7E3 Fab (n = 30)		Placebo (n = 30)	
TIMI flow	B	A	B	A
0	1	1	4	3
1	2	1	0	1
2	10	5	7	6
3	17	23	19	20
Improved		6		4
Worsened		0		3
Intracoronary filling defect	5	2	1	1

B = before study drug infusion; A = after study drug infusion.

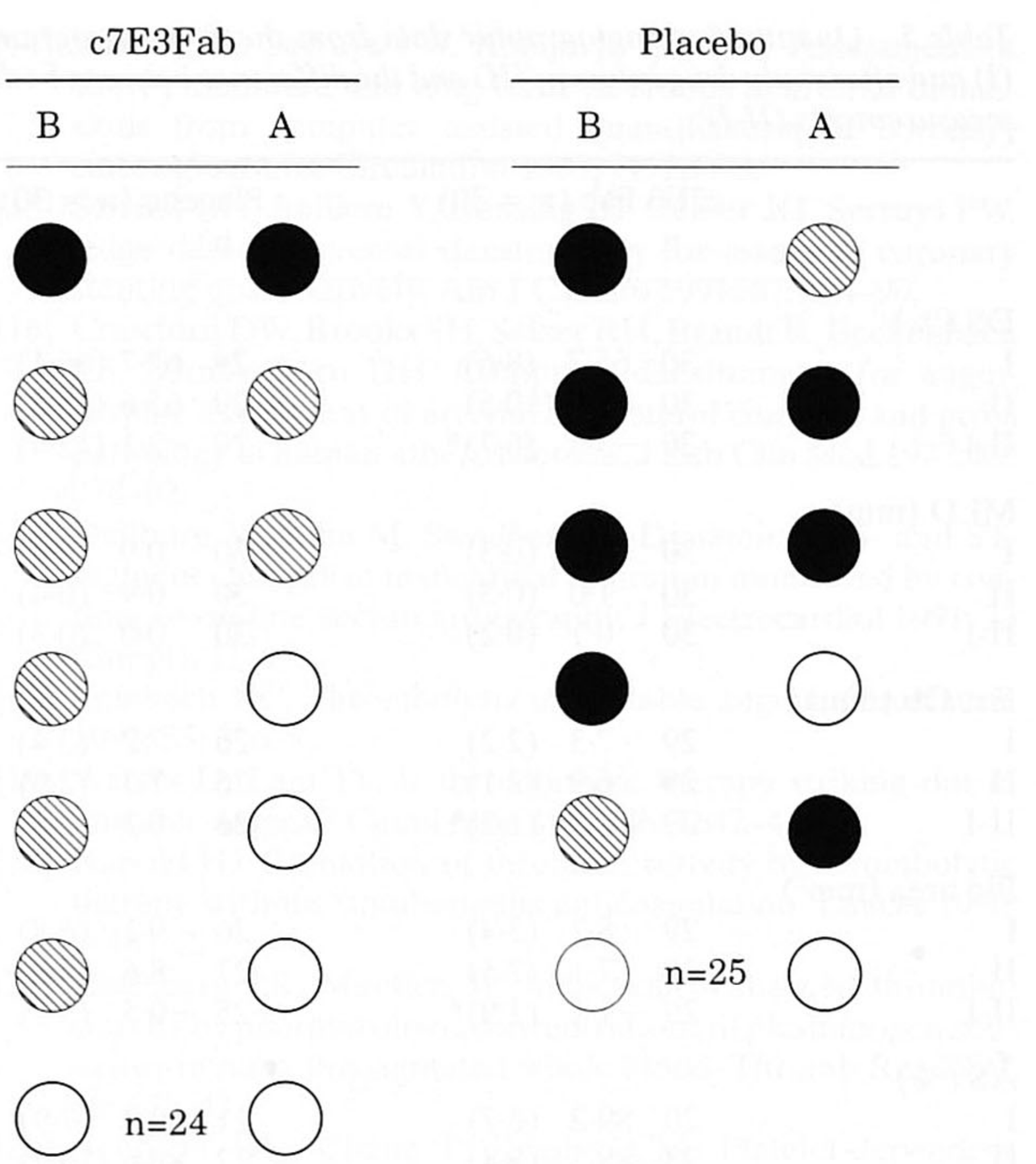

Figure 1 Qualitative coronary angiographic data of the ischaemia-related coronary artery before (B) and after (A) study drug infusion. ● = totally occluded coronary artery; ⊘ = intracoronary filling defect; ○ = patent coronary artery, without filling defect. Note: The number of patent vessels with no filling defect in either angiogram is depicted in the bottom line.

thrombotic remnants. Three out of five coronary clots resolved in the c7E3 group.

QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS

Quantitative coronary angiographic data are summarized in Table 5. In one patient with a very proximal left anterior descending coronary artery lesion calculation of percentage diameter stenosis was not possible because the reference diameter could not be ascertained. Plaque area and extent of obstruction could only be calculated in patent coronary arteries. A significant decrease in percentage diameter stenosis, extent of obstruction and plaque area was observed in the c7E3 Fab patients. In the placebo group, similar changes were observed to a lesser extent, except for the extent of obstruction, which increased in the placebo group patients. Differences between groups were not significant.

ANGIOPLASTY PROCEDURE

Angioplasty was performed in all 60 patients. In one patient who received c7E3 Fab, PTCA was deferred because of a total occlusion from a large intracoronary clot at the second angiogram. He was treated with intracoronary alteplase 50 mg infused over 30 min, followed by 50 mg intravenously over 2 h. 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

Table 5 Quantitative angiographic data from the first angiogram (I) and after study drug infusion (II) and the difference between both measurements (II-I)

	c7E3 Fab (n = 30)			Placebo (n = 30)		
	n			n		
DS (%)						
I	30	65·7	(8·6)	29	67·7	(16·1)
II	30	62·3	(10·5)	29	65·6	(15·8)
II-I	30	−3·4	(6·7)*	29	−2·1	(12·4)
MLD (mm)						
I	30	0·9	(0·3)	30	0·9	(0·4)
II	30	1·0	(0·3)	30	0·9	(0·4)
II-I	30	0·1	(0·2)	30	0·0	(0·3)
Ext Ob (mm)						
I	29	7·3	(2·2)	26	7·2	(3·4)
II	29	6·9	(2·1)	26	7·3	(2·9)
II-I	29	−0·5	(1·2)*	26	0·3	(1·8)
Plq area (mm^2)						
I	29	8·2	(3·4)	26	9·1	(6·8)
II	29	7·1	(2·5)	27	8·6	(4·8)
II-I	29	−1·1	(1·9)*	25	−0·5	(3·3)
AS (%)						
I	20	89·2	(6·7)	21	90·7	(7·9)
II	23	88·3	(8·4)	22	89·6	(10·2)
II-I	19	1·8	(8·1)	19	−1·3	(6·4)

DS = diameter stenosis; MLD = minimal lumen diameter; Ext Ob = extent of the obstruction; Plq area = plaque area; AS = area stenosis; *$P \leq 0{\cdot}05$ 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.

total success rate of the angioplasty procedure was 83% in the c7E3 Fab group and 70% in the placebo group (Table 6).

Discussion

Two recent editorials addressed the relative inefficacy of thrombolytic agents in patients with unstable angina[18,19]. The apparent discrepancy between the effects of thrombolytic agents in myocardial infarction and unstable angina pectoris are explained by the difference in underlying disease and enhanced thrombus formation. Opening of an occluded artery in myocardial infarction, and keeping an artery open in unstable angina require different approaches.

Table 6 Complications and untoward events during and after coronary angioplasty

n	c7Ee Fab 30	Placebo 30
Mortality	0	1
Myocardial necrosis	1	3
Urgent CABG	0	3
Re-PTCA	0	2
Residual stenosis >50%	4	6
Number of patients with one or more untoward events	5	9
Procedural success (%)	83	70

CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

Several studies suggest that thrombolytic therapy might enhance thrombin formation and activate platelets to further coronary thrombosis[20–26]. These effects of tissue plasminogen activator (rt-PA) can be countered by the monoclonal antiplatelet GPIIb/IIIa receptor antibody, as has been demonstrated in a canine model[27]. In two patients treated with c7E3 in this study, administration of rt-PA helped to resolve large clots, without untoward effects.

It is conceivable that the c7E3 antibody prevents platelet aggregation and occlusion of coronary arteries in unstable angina. The present pilot study supports the concept that treatment with c7E3 Fab in patients with refractory unstable angina reduces recurrent ischaemic episodes and facilitates PTCA. In 30 patients treated with placebo, seven (23%) had a total of 12 events. In contrast, only one of the 30 patients treated with c7E3 Fab had a single event (3%, $P = 0.03$). Recurrent ischaemia during the 18 to 24 h of treatment before PTCA was reduced by 44% ($P = 0.06$) in patients receiving c7E3 Fab, and the severity of the culprit lesion was improved (Table 5). 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[28]. Urgent PTCA in such patients has been associated with a 10% to 15% complication rate[28]. A similarly high complication rate was observed in the placebo group.

OTHER PATIENT STUDIES WITH 7E3 ANTIBODIES

Open-label non-randomized studies with murine (m) c7E3 $F(ab')_2$ and 7E3 Fab suggested 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 min), but returned in several patients when the bleeding time was normalized[11]. More recently, Kleiman *et al.*[29] reported better coronary artery patency and a trend for fewer ischaemic 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 not associated with a higher bleeding risk. In a recently presented trial of 2099 patients undergoing 'high-risk' angioplasty, a single bolus of c7E3 Fab did not prevent recurrent ischaemic events[30]. In that trial, a marked reduction of events was reported during and after bolus injection followed by 12 h of infusion of c7E3 Fab at the same dosage as in the present pilot study.

At 6 months follow-up a significant reduction in the number of repeat revascularization procedures in the same group was noted[31]. In the present study, c7E3 Fab was administered for at least 18 h before PTCA. One hour after PTCA, the drug was discontinued to allow sheath removal. These two studies indicate that prolonged (≥12 h) inhibition of platelet aggregation either before or after PTCA[30] will be necessary to prevent ischaemic events in patients with an unstable coronary plaque. Additional studies are required to assess the optimal timing and duration of therapy with c7E3 Fab in different patient populations.

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 favourable course, with less recurrent ischaemia, 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. However, these data indicate that potent inhibition of platelet aggregation may be of particular clinical value in patients with refractory unstable angina who undergo PTCA.

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