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The Effect of Blockade of the CD11/CD18 Integrin Receptor on Infarct Size in Patients With Acute Myocardial Infarction Treated With Direct Angioplasty: The Results of the HALT-MI Study

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OBJECTIVES The purpose of this study was to determine whether Hu23F2G (LeukoArrest), an antibody to the CD11/CD18 integrin receptors, would reduce infarct size in patients undergoing primary angioplasty for an acute myocardial infarction.

BACKGROUND Reperfusion injury in acute myocardial infarction has been shown experimentally to be related to neutrophil accumulation. Inhibitors of the CD11/CD18 or CD18 integrin receptors have been shown to reduce infarct size in experimental models.

METHODS Patients within 6 h of onset of chest pain with ST-segment elevation were randomized to receive either 0.3 mg/kg or 1.0 mg/kg of Hu23F2G or placebo just before angioplasty of occluded arteries (Thrombolysis in Myocardial Infarction TIMI flow grade 0 or 1). The primary end point was infarct size as measured by sestamibi single-photon emission computed tomography (SPECT) scan five to nine days later.

RESULTS Four-hundred and twenty patients were enrolled and received a placebo or the study drug. The groups did not differ in baseline or angiographic characteristics or angioplasty results. Infarct size was 16%, 17.2% and 16.6%, for placebo, 0.3 mg/kg and 1.0 mg/kg, respectively, of the left ventricle (p = NS). No differences were evident in those patients with anterior myocardial infarction or those presenting within 2 h of onset of chest pain. Corrected TIMI frame count was also not different between groups. Clinical events at 30 days were very low, with a mortality of 0.8%, 1.4% and 3.3%, respectively. The drug was well tolerated, with a slight increase in minor infections in the high dose group.

CONCLUSIONS The results of this multicenter, double-blind, placebo-controlled, randomized clinical trial demonstrated that an antibody to CD11/CD18 leukocyte integrin receptor did not reduce infarct size in patients who underwent primary angioplasty. (J Am Coll Cardiol 2002;40: 1199–204i) © 2002 by the American College of Cardiology Foundation

Reperfusion therapy reduces infarct size, but reperfusion injury may limit its benefits (1–8). Experimental studies have demonstrated that the inhibition of the CD11/CD18 leukocyte integrin receptor can result in a significant reduction of infarct size (9–14). In addition, inhibition can improve endothelial function, coronary blood flow and left ventricular hemodynamics. Hu23F2G (LeukArrest) is a humanized antibody directed against all isoforms of the CD11/CD18 integrin receptor (15). It has been shown to inhibit the attachment and transmigration of neutrophils, as well as adhesion-mediated release of oxygen-free radicals in vitro (oral communication, ICOS Corp., October 1997).

This multicenter, randomized, double-blind study was undertaken to evaluate the safety and efficacy of Hu23F2G in reducing infarct size as determined by sestamibi single-photon emission computed tomography (SPECT) scanning in patients with ST-segment elevation acute myocardial infarction (MI) undergoing primary angioplasty.

METHODS

This study was conducted at 54 study centers in the U.S. that were capable of performing primary angioplasty (see complete Appendix 1 online at www.cardiosource.com/jacc.html). Patients were eligible for participation if they were between the ages of 18 and 85, had chest pain or other typical signs or symptoms of acute MI of less than 6 h in duration and were candidates for primary angioplasty. For anterior MI, the electrocardiogram (ECG) entry criteria were ST-segment elevation of at least 2 mm in at least two contiguous precordial leads or new left bundle branch block. For inferior MI, the ECG entry criteria were at least 1-mm ST-segment elevation in two or more inferior limb leads (II, III, AVF), with reciprocal ST depression of at least 0.5 mm in two or more precordial leads. Patients were excluded if they had a history and ECG evidence of previous Q-wave MI or an ECG pattern that made the diagnosis of MI difficult. Other exclusion criteria were cardiogenic shock,

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Abbreviations and Acronyms

CK-MB = creatnine kinase-MB fraction (primarily in cardiac muscle)
ECG = electrocardiogram
MI = myocardial infarction
SPECT = single-photon emission tomography
TIMI = Thrombolysis In Myocardial Infarction

treatment with thrombolytic therapy before study drug administration, a baseline serum creatinine of >2 mg/dl, evidence of an ongoing bacterial infection, pregnancy and the presence of other serious medical conditions.

After informed consent, patients were randomized into the study and then immediately taken to the cardiac catheterization laboratory, where coronary angiography was performed and Thrombolysis In Myocardial Infarction (TIMI) flow grade determined. The infarct-related artery was initially injected to determine TIMI flow just before the administration of the study drug (16). Subsequently, multiple views of both coronary arteries were obtained after intracoronary nitroglycerin administration. Care was taken to ensure that the entire vessel and catheter was visualized to calculate TIMI frame count. If the infarct artery showed TIMI 0 or 1 flow grade, the patient was enrolled into the study. Patients who showed TIMI 2 or 3 flow grade did not receive the study drug but had complete screening data obtained. The study drug was administered as a weight-adjusted, intravenous bolus over 1 to 2 min. Patients were randomized to receive either 0.3 mg/kg or 1 mg/kg of Hu23F2G IV or placebo. Previous studies in normal volunteers have shown that these doses resulted in an 80% saturation of the CD11/CD18 receptor for 12 to 24 h. These doses, however, were lower than those shown to be neuroprotective in experimental studies (that is, 4 mg/kg). All patients received aspirin and heparin that was administered by intravenous infusion to maintain the activated clotting time between 250 and 300 s. Angiography was performed using standardized techniques of angioplasty with initial passage of a guidewire and balloon dilation. The use of glycoprotein IIb/IIIa antagonists was permitted, as was the use of coronary stents or other devices, at the discretion of the operator. Only the infarct-related artery was treated.

After the procedure, the sheaths were removed. The patients were then treated in the Coronary Care Unit. The institution of angiotensin-converting enzyme inhibitors, beta-blockers and platelet antagonists such as ticlopidine or clopidogrel were used at the discretion of the investigator.

Five to nine days after the administration of the study drug, a technetium-99m sestamibi SPECT image was obtained. Patients were discharged from the hospital, and they returned for an outpatient visit at 30 days for clinical assessment and determination of adverse events. At 6 months, the patients were contacted by telephone to determine their vital status and the need for rehospitalization and follow-up procedures.

Nuclear imaging technique. The nuclear core laboratory (Mayo Clinic Foundation, Rochester, Minnesota) initially validated adequate image quality at each site using a cardiac phantom and a quality control test (17). Those centers with single-headed cameras were required to use either a step-and-shoot mode or a continuous mode in circular orbit. Thirty images were required in a 64- × 64-word mode matrix over a 180° arc, beginning at 45° right anterior oblique and ending in the left posterior oblique position, with an image time of greater than 40 s. For multihead SPECT systems, acquisition was performed over 360° every 6°. Data were stored in 64- × 64-word mode matrix with an image time of greater than 30 s. Raw unprocessed data, the most recent 30 M count flood images and the most recent center of rotation study were forwarded to the core laboratory, which was blinded to treatment assignment. Measurement of infarct size has been described and validated previously (17–19). Quantitation of the extent of left ventricle with absent perfusion was performed using a five-slice technique, with short axis slices obtained every 6 mm. Quantitation was performed using threshold techniques and standard geometrical formulas. Infarct size was expressed as the percent of left ventricle with a perfusion defect.

Core angiographic laboratory. The core angiographic laboratory (University of Washington, Seattle) blindly reviewed all angiograms. The TIMI flow and corrected TIMI frame counts were determined as previously defined (16). Quantification of the coronary stenoses was performed by two readers who had no knowledge of the treatment assignment. Collaterals to the infarct-related artery were graded as present or absent. If present, the degree of perfusion was graded as full if the entire vessel was visualized and partial if only a portion of the vessel was visualized.

Safety monitoring. A safety summary was faxed to the coordinating center on day 9 or at hospital discharge. An Independent Data and Safety Monitoring Committee periodically reviewed the status of the trial.

Statistical analysis. The sample size was calculated to detect a reduction in infarct size of 8.5% of the left ventricle in patients with anterior MI and a reduction of 3.3% in patients with inferior MI. Using the variability reported elsewhere for similar patients (18,19), 112 patients per treatment group were required for two-sided p value of <0.05 at 80% power. Assuming the loss of patients during the study, 140 patients per treatment group were randomized.

The primary analyses were performed using the intention to treat the population; the results were also analyzed according to the treatment they actually received. Analyses of variance was used for comparing baseline characteristics across groups for continuous variables. The Fisher exact test was used for comparing treatment groups for categorical variables.

For the primary efficacy end point, myocardial infarct

Table 1. HALT-MI: Demographics and Baseline Characteristics

	Hu23F2G		
	0.3 mg/kg (n = 128)	1 mg/kg (n = 139)	Placebo (n = 153)
Mean age (yrs)	60.4	59.8	60.2
Percent male	73	74	69
Caucasian (%)	89	83	85
Infarct location			
Anterior (%)	33	36	34
Inferior/other (%)	67	64	66
Mean time chest pain to hospital (h)	1.66	1.70	1.71
Mean time chest pain to balloon (h)	3.9	3.7	3.7
Medical history			
Prior MI (%)	13	12	13
Hypertension (%)	50	48	48
Hypercholesterolemia (%)	44	35	44
Cigarette smoker (%)	67	78	67
Prior stent placement (%)	3	3	5
Prior PTCA/atherectomy (%)	9	7	12
Prior CABG (%)	9	4	3
Diabetes (%)	20	17	17

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

size, determined by technetium-99m sestamibi SPECT imaging, was compared using analysis of co-variance. The following variables were used as covariates: area under the curve for the first 6 h of creatine kinase-MB fraction (CK-MB), time between initial symptoms and first balloon deflation, age, gender, pretreatment TIMI flow and infarct location. The primary analysis used imputed values for missing data. Patients who died before imaging (n = 8) were assigned the largest infarct size measured for that infarct location (anterior or other) for each patient. For patients who were alive but who did not obtain a follow-up SPECT image (n = 22), the median value measured for each infarct location was used. A Cox proportional hazards regression model was used for the survival analysis.

RESULTS

Patient population. Six-hundred and thirty-seven patients were randomized and 420 patients with TIMI flow grade 0 or 1 flow were enrolled. One-hundred and sixty-nine patients of 214 did not receive study drug because of their TIMI 2 or 3 flow grade at initial angiography. One hundred and twenty-eight received 0.3 mg/kg of LeukoArrest, 139 patients received 1 mg/kg of LeukoArrest and 157 patients received placebo. The follow-up was complete at 30 days in 99% of patients. Fourteen patients (seven from the placebo group) received a different therapy than initially assigned.

Baseline characteristics. The baseline demographic and clinical characteristics of the 420 patients enrolled were not different between groups receiving the study drug versus the placebo (Table 1). Medication use during hospitalization was not different between groups. The angiographic findings showed the infarct artery to be the left anterior descending in 33% to 36% (Table 2). TIMI 0 or 1 flow grade was confirmed by subsequent core angiographic lab assessment in 96% to 98% of patients. Collateral vessels were present to the infarct related artery in 32% to 40% of patients. Full collateralization was present in 29% to 37% percent of those who had collaterals.

Table 2. HALT-MI: Angiographic and Angioplasty Results

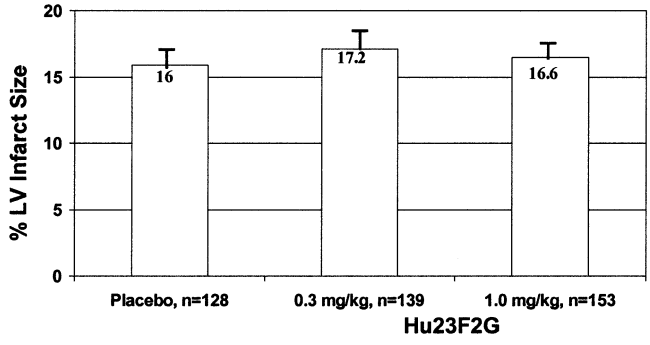
	Hu23F2G		
	0.3 mg/kg (n = 128)	1 mg/kg (n = 139)	Placebo (n = 153)
Infarct vessel			
LAD (%)	34	36	34
Circumflex (%)	14	13	9
RCA (%)	52	51	57
TIMI flow pre-PTCA (%)			
0–1	98	96	96
2	2	4	3
Collaterals to IRA (%)	32	42	41
Angiographic success	88	86	89
Percent residual stenosis	8	6	8
TIMI flow-post (%)			
0–1	6	6	4
2	9	4	8
3	81	86	86
Corrected TIMI frame count	21.3	23.3	22.3

IRA = infarct-related artery; LAD = left anterior descending; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; TIMI = Thrombolysis In Myocardial Infarction.

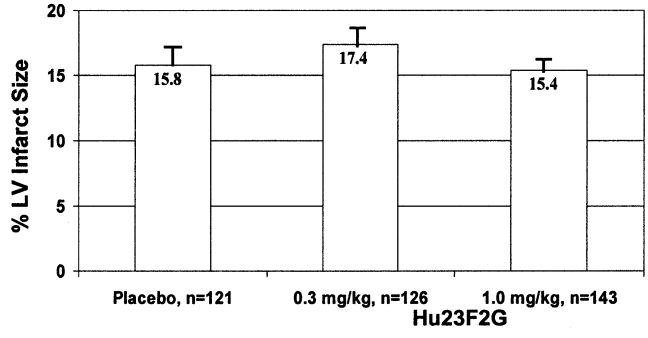
Angioplasty results. A successful procedure, defined as less than a 50% residual stenosis without death or emergency bypass surgery, was seen in 86% to 89% of each group (Table 2). Stents were placed in 85% of patients and abciximab was used in 65% to 73% of patients. The residual stenosis was less than 9% in all three groups; TIMI 3 flow grade was established in 81% to 86% of patients. None of the differences among the three groups were statistically significant.

Infarct size. The final infarct size for the intention-to-treat population, with and without imputation, is shown in Figure 1A and 1B. Including imputed values for missing data, infarct size was 16%, 17.2% and 16.6% of the left ventricle for placebo, 0.3 mg/kg and 1 mg/kg, respectively (p = 0.796). The observed data (without imputation) on 390 patients (92.9% of the study group) gave similar results.

The subgroup of patients with anterior MI had significantly greater infarct size (averaging 25%), but again no differences were noted among the three groups. Likewise, when patients were subdivided by the time from the onset of chest pain to balloon deflation or by the presence of collaterals, there were no differences. Infarct size, measured by CK-MB area under the curve for 24 h, was not different among the three groups (175%, 175% and 184% per hour for placebo, 0.3 mg/kg and 1 mg/kg, respectively). Microvascular flow, assessed by corrected TIMI frame counts, were also not different among the groups (21.3%, 23.2% and 22.3%, respectively).



A Imputed Values, Mean ± SE



B Observed Data, Mean ± SE

Figure 1. (A and B) HALT-MI infarct size by single-photon emission computed tomography, imputed values and observed data. LV = left ventricular.

Clinical events at 30 days. The incidence of major clinical events was very low, with only eight deaths in the study population, for an overall 30-day mortality of 1.9% (Table 3). Although there were fewer deaths and reinfarctions in the low dose group (0.3 mg/kg) and survival at 30 days tended to be better in the treatment groups, there was no significant statistical difference ($p = 0.20$), given the low number of events. When a composite end point using death, new MI, rehospitalization for heart failure and infarct size by SPECT scanning were used, no differences between groups could be discerned.

Adverse events. Major infections occurred in 5% to 10% of patients, with minor infections in 2% to 9%. The most frequent infection was urinary tract infection, which occurred in 6.3%, 9.4% and 2.6% of patients in the 0.3 mg/kg, 1 mg/kg and placebo group, respectively. Infections were more common in the active treatment group but were easily managed and caused no serious adverse events.

Table 3. HALT-MI: Clinical and Adverse Events at 30 Days

Event	Hu23F2G 0.3 mg/kg (n = 128)	Hu23F2G 1 mg/kg (n = 139)	Placebo (n = 153)
Clinical events			
Death (%)	0.8	1.4	3.3
Reinfarction (%)	0.8	2.9	3.9
New CHF (%)	1.6	1.4	3.3
Revascularization (%)	12.5	17.3	10.5
Rehospitalization (%)	8.6	10.1	13
Adverse events			
Major infection (%)	6	10	5
Minor infection (%)	5	9	2
Bleeding (%)	16	17	15

CHF = congestive heart failure.

DISCUSSION

The results of this multicenter, randomized, double-blind, placebo-controlled, parallel group study demonstrated that Hu23F2G, an antibody directed against the leukocyte CD11/CD18 integrin receptor, did not significantly reduce infarct size, as determined by Tc-99m sestamibi SPECT scanning five to nine days after primary angioplasty. The drug was well tolerated in this study population, although infections were slightly more common in the high dose group.

Neutrophils in reperfusion injury. Reperfusion of ischemic myocardium, particularly with oxygenated perfusate, has been shown to contribute to further tissue damage and has been called reperfusion injury (4–8). A number of mechanisms have been proposed for reperfusion injury, including an excess release of oxygen free radicals. Inflammation during acute MI has been recognized for more than 60 years (20). Experimental and clinical studies have demonstrated an increase in neutrophil accumulation in the infarct zone upon reperfusion, with an increase in cytokine release and expression of the CD11/CD18 integrin receptors on white cells (21–24) before, but particularly after, reperfusion, with the plugging of small arterioles and capillaries (25). Clinical estimation of microvascular flow after reperfusion using the rate of resolution of ST-segment changes, corrected TIMI frame count, or the density of myocardial contrast has identified patients at higher risk for subsequent cardiovascular events (26–28).

Inhibitors of the CD11/CD18 integrin receptor. Antibodies to either all or one of the four isoforms of the CD11/CD18 integrin receptor have been shown to reduce infarct size, improve coronary blood flow, improve left ventricular function and decrease neutrophil infiltration (9–14).

Hu23F2G (LeukArrest), a humanized antibody against all four leukocyte integrins, has been shown to inhibit leukocyte attachment and transmigration (15). In normal volunteers, a greater than 80% saturation of the CD11/CD18 neutrophil receptor inhibited chemotaxis of granulocytes using a skin chamber (personal communication, ICOS Corp.). In a pilot study of 60 patients undergoing primary angioplasty with acute MI, using the same doses as used in this study, an 80% saturation of the receptor was demonstrated from 24 to 48 h (29). Given the negative results of this study, it is possible that this degree of saturation of neutrophil CD11/CD18 receptors is insufficient to reduce infarct size. It is possible that the use of GP IIb/IIIa agents in this study may have influenced the results. Some studies have suggested that abciximab inhibits the

MAC-1 receptor, and this may have similar effects to LeukArrest (30). The results of the Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) trial, which used an antibody against the CD18 receptor in patients with acute MI receiving thrombolysis, also failed to show a significant difference in infarct size as measured by Tc-99m sestamibi or TIMI flow (31).

Other agents to reduce reperfusion injury. Clinical trials of many other agents directed toward reducing reperfusion injury have been similarly disappointing. Prostacyclin, fluosol, magnesium, poloxmer 188 (rheothrx) and tremetazidine have also failed to reduce infarct size in randomized clinical trials (32–34) (M. Marzilli, unpublished data). In contrast, adenosine has shown promise (35,36). Adenosine is a potent vasodilator that also has cardioprotective properties, most likely through the replenishment of high-energy phosphate stores, inhibition of oxygen-free radicals, inhibition of neutrophils and improvement of microvascular flow and ischemic preconditioning (36). The Acute Myocardial Infarction Study of Adenosine (AMISTAD) study showed a 33% reduction in infarct size, particularly in patients with anterior MI (15% vs. 45.5%), when given to patients at the time of thrombolysis (35). In contrast to the AMISTAD study, this study had a very low incidence of complications and death. This could be due to the effectiveness of primary angioplasty in the treatment of acute MI and/or other variables, such as patient selection. Although the sites chosen to participate in the study had considerable clinical experience in primary angioplasty, the majority were not academic medical centers. Therefore, the results are likely to reflect the contemporary practice of primary angioplasty in patients with their first ST elevation infarction.

Study limitations. This study was sized to demonstrate a decrease in infarct size of 8.5% of the left ventricle in anterior MI and a decrease of 3.2% in inferior MI. The design assumptions were fairly well satisfied, with an 80% power. However, the study was underpowered to detect a smaller degree of benefit. Because the area at risk was not measured, it is possible that measurement of myocardial salvage would have been a more sensitive measure than final infarct size. Previous studies, however, have shown a close relationship between the two (18), and the logistical issues led to the decision not to determine myocardial salvage. The dose was chosen to insure at least 80% granulocyte receptor saturation for 12 to 24 h, which in Phase 1 studies in normal volunteers resulted in a significant inhibition of chemotaxis, using a skin window study. However, the dose of drugs and the timing of administration may not have been sufficient to inhibit the intense neutrophil accumulation known to occur during acute MI. Experimental studies have shown that higher doses are necessary to demonstrate neuroprotection. Although infarct size has been established as a surrogate end point for acute MI trials (19), it is possible that the therapy might have clinical benefits independent of infarct size, which might have been detected in a much larger trial using clinical end points.

Conclusions. The results of the multicenter, randomized trial demonstrate that an antibody to the CD11/CD18 leukocyte integrin receptor did not reduce infarct size in patients undergoing primary angioplasty. Ongoing studies of other leukocyte integrin receptor blockers will help to better define the role of neutrophil inhibition in reducing infarct size.

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APPENDIX

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