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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

Glycoprotein IIb/IIIa Receptor Blockade in Myocardial Infarction

Presented by: E.J. TOPOL, MD, M.L. SIMOONS, MD, J. ADGEY, MD, D.J. KEREIAKES, MD

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Reported and discussed by:
ANATOLY LANGER, MD

Platelet aggregation is a key step in coronary thrombus formation, particularly in relation to plaque rupture and the pathogenesis of acute ischemic syndromes. Accumulating evidence continues to suggest that inhibition of the glycoprotein IIb/IIIa receptor has a pivotal role in the management of patients with acute ischemic syndromes or those undergoing percutaneous revascularization. The only glycoprotein IIb/IIIa receptor antagonist approved for use in Canada is abciximab (ReoPro), which is given intravenously. Abciximab has clearly been shown to reduce short- and long-term unfavourable events in patients undergoing angioplasty, particularly in the setting of unstable angina. Additional discussion at the satellite symposium provided new information and further insight into the use of abciximab.

We have previously reported the results of EPIC, EPILOG, and CAPTURE trials, which showed that patients who have high-risk angioplasty, recurrent ischemia, or percutaneous revascularization significantly benefit from the use of abciximab.[1-3] A number of recently completed investigations have studied the use of abciximab in patients with acute myocardial infarction (MI). While it is clear that abciximab may be administered in patients with acute MI as part of the preparation for direct angioplasty, other issues with regard to thrombolytic administration, especially dose considerations, remain less clear.

RAPPORT study

This study addressed the use of abciximab in acute MI in the setting of primary percutaneous transluminal coronary angioplasty (PTCA). Presentation of final results is expected in November 1997 at the American Heart Association meeting. The study involved 39 U.S. centers. Patients with acute MI and ST elevation were randomized within 12 hours of presentation to either bolus and infusion of abciximab vs. placebo in the setting of primary PTCA. It is important to note that the use of stents was discouraged and that heparin was administered at the high dose of 100 IU/kg.

Baseline comparison did not reveal any significant differences between 242 patients in the control group and 241 patients who received abciximab. Similarly, no difference in clinical characteristics was apparent in patients who actually received the drug. Both study groups had a high dropout rate: 72 patients in the control group, reducing its size to 169 patients; 62 in the abciximab group, leaving 179 patients in this arm. Intention-to-treat analyses of those who received the drug and those who received percutaneous revascularization were conducted. About 10% of patients did not need PTCA after initial angiography.

Pretreatment patency assessment revealed TIMI III flow in only 7.7% of patients in placebo arm and 14.0% of those receiving abciximab (p=0.053). Not surprisingly, post-treatment patency was high in both groups because of PTCA (85.2% in placebo group; 87.0% in abciximab group).

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

Table 1: Intention-to-treat analysis

	7 days		30 days	
	placebo	abciximab	placebo	abciximab
Death (%)	1.7	1.2	2.1	2.5
Reinfarction (%)	3.3	1.7	4.1	3.3
Emergency PTCA (%)	4.1	1.2	5.4	1.7

PTCA=percutaneous transluminal coronary angioplasty

There was a significant reduction in the composite endpoint of death, reinfarction, and emergency percutaneous revascularization at 7 days and at 30 days (Table 1).

It is important to note that all major subgroups of patients derived similar benefit from abciximab. Analysis of a 30-day composite endpoint, based on only patients who received study medication revealed similar and significant benefits (Table 2).

Finally, a comparison of treatment limited to patients who underwent PTCA showed a significant benefit with abciximab (Table 3).

The use of stents was reduced by about 33% in the abciximab group.

While no intracranial bleeding had occurred, major bleeding was more frequent with abciximab (16.6%) as compared to placebo (9.5%, p=0.02). Similarly, transfusion requirements were higher with abciximab (13.7%) as compared to placebo (7.9%, p<0.05).

Excessive bleeding and the need for transfusions was related to the vascular access site and, to a much lesser degree, GI bleeding. Clearly, part of the reason for excessive bleeding at the vascular access site was due to the use of high-dose heparin and late removal of sheaths, which occurred, on average, about 20 hours after the procedure. Further subanalysis of bleeding complications revealed that the most significant excessive bleeding occurred in patients with an activated coagulation time (ACT) of ≥350 seconds.

The results of RAPPORT, the only study clearly dedicated to the use of abciximab in patients with acute MI, reveals almost a 70% reduction in the need for emergency PTCA and a 74% reduction in the composite endpoint of death, reinfarction, and emergency PTCA. These results complement previous results involving the use of this agent (Table 4).

The benefits of abciximab, as compared to other glycoprotein IIb/IIIa inhibitors, continues to be studied. Future trials may examine how prolonged drug availability affects platelets and how the nonspecific inhibition of abciximab affects the vitronectin receptor. However, the results of PRISM, PRISM Plus, and PURSUIT studies presented at this meeting suggest that benefits from glycoprotein IIb/IIIa inhibition extend to noninterventional subgroups and may represent a class effect of these agents.

Is abciximab equivalent to stenting?

As optimal management of patients with acute ischemic syndromes and stable coronary artery disease (CAD) continues to evolve, it may be useful to compare recent clinical trials of glycoprotein IIb/IIIa antiplatelet drugs, e.g., EPILOG[2], CAPTURE[3], and the practice of stenting, e.g., BENESTENT II.

Patients in BENESTENT II, compared to those in EPILOG or CAPTURE, had fewer factors associated with poor outcome, including female gender, acute unstable angina, complex clinical history, and smaller target-vessel diameter.

After 6 months of follow-up, there was a significant reduction in the hard endpoints of death and reinfarction in patients treated with abciximab, compared to placebo (Table 5).

Table 2: Efficacy analysis

	placebo	abciximab
Death (%)	1.9	1.8
Reinfarction (%)	4.7	2.7
Emergency PTCA (%)	5.6	1.8
Composite endpoint (%)	10.3	4.9*

*p≤0.05

PTCA=percutaneous transluminal coronary angioplasty

Table 3: 30-day Composite Endpoint in Patients with PTCA

	placebo	abciximab
Death (%)	1.8	1.1
Reinfarction (%)	5.3	0.6
Emergency PTCA (%)	5.3	0.7
Composite endpoint (%)	10.1	2.8*

*p≤0.05

PTCA=percutaneous transluminal coronary angioplasty

No significant reduction in death or MI was seen with the use of stenting in BENESTENT II (4.4% for PTCA vs. 4.3% for stent, p=ns). On the other hand, the use of stents significantly benefited patients who had repeat PTCA (18.9% with PTCA vs. 12.8% with stent, p≤0.05), while no benefit was seen for repeat PTCA in EPILOG or CAPTURE. However, a significant reduction in repeat PTCA was seen in the EPIC study at 6 months.[1] This benefit has reportedly continued up to 3 years.[4]

It would seem that the prevention of thrombosis and reduction in MI and mortality are the primary goals of treatment with abciximab in all subsets of patients undergoing PTCA, while stenting is associated with a greater luminal diameter and, therefore, lower incidence of reintervention.

We have learned to better manage complications associated with the use of antiplatelet therapy and stenting, especially excessive bleeding. For example, excessive bleeding was significantly higher in patients receiving abciximab in EPIC and CAPTURE but not in EPILOG, where the dosage of heparin was reduced in a weight-adjusted manner and the puncture site received better care. Comparison of BENESTENT II and BENESTENT I studies also shows a reduction in bleeding complications associated with better stent deployment and effective use of Aspirin® and ticlopidine combinations instead of long-term anticoagulant therapy.[5]

We continue to refine our management strategies in patients with acute and stable ischemic syndromes by the comparative assessment of large clinical trials.

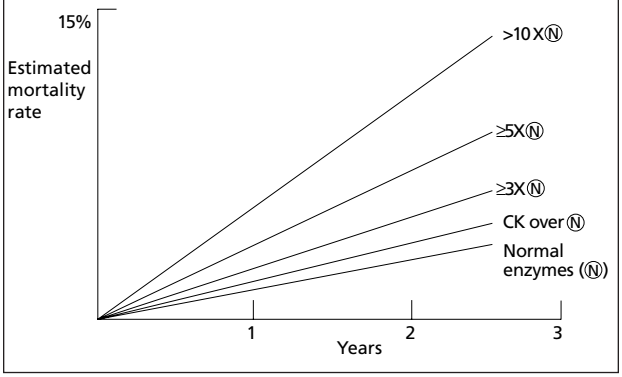
CK elevation: Long-term impact?

There is a general perception that small elevations in creatine kinase (CK), e.g., twice the normal limit, occur in only 3-4% of patients who have PTCA. These elevations are not usually associated with significant long-term sequelae and are thought to be artifactual in nature. However, when careful and systematic measurement is undertaken, the actual frequency of CK elevation is 2-3 times greater. In fact, recent results of studies of patients with PTCA (STARS) and atherectomy (CAVEAT I and II, BOAT)[6-8] suggest that the incidence of CK elevation and non-Q-wave MI may be as high as 20%.

Table 4: 30-day composite endpoint

	placebo	abciximab	p value
EPIC (%)	12.9	8.3	≤0.05
EPILOG (%)	11.7	5.3	≤0.05
CAPTURE (%)	15.9	11.3	≤0.05
RAPPORT (%)	9.9	5.8	≤0.05
Pooled results (%)	12.8	7.0	≤0.05

Figure 1: Schematic graphic of periprocedural CK elevation and mortality



Further analysis of long-term sequelae suggests that late death in patients with normal CK after intervention occurs in only 1-2% of patients, while in those with an elevated CK, the incidence is 6-7% (Figure 1). This finding suggests that CK elevation is indicative of myocardial necrosis, although the mechanism of action is not well understood.

One proposed mechanism involves distal embolization and microvascular occlusion, which may be reduced by the concurrent use of antiplatelet drugs and may explain the reduction of death and MI in abciximab-treated patients undergoing PTCA. For example, the results of EPILOG show a significant reduction of non-Q-wave MI, which was significantly greater than the reduction in Q-wave MI. Importantly, both large and small non-Q-wave MI were reduced when abciximab was used with PTCA.

Meta-analysis of stented patients in EPIC, EPILOG, and CAPTURE studies shows a reduction in the composite endpoint of death, reinfarction, and repeat emergency PTCA from 20.4% in 221 placebo-treated patients to 8.5% in 308 patients who received abciximab (p≤0.05).

Future of glycoprotein IIb/IIIa blockers

The use of abciximab has significantly changed how patients with unstable angina are managed. An unpublished study of 321 consecutive patients who presented with

Table 5: 6-month composite endpoint

	placebo	abciximab	p value
EPIC	12.8	8.9	≤0.05
EPILOG	11.1	6.1	≤0.05
CAPTURE	10.9	9.0	≤0.05
Combined endpoint	11.2	7.2	≤0.05

unstable angina shows that the majority were discharged within 48 hours and had a low incidence of periprocedural complications: mortality, 0.3%; emergency bypass surgery, 0.6%; emergency PTCA, 0.9%; and Q-wave MI, 0.6%.

Further studies are clearly needed to identify the role of other intravenous glycoprotein IIb/IIIa inhibitors, such as tirofiban, which has been studied in patients with acute ischemic syndromes (PRISM and PRISM Plus), or integrelin (PURSUIT), and the importance of long-term inhibition with oral agents.

The success of abciximab, when used in conjunction with PTCA, has expanded its application to patients with acute ischemic cerebrovascular disease. The efficacy of abciximab in patients who present within 12 hours of acute stroke is the subject of an ongoing, large, multicentre international study (RECOVER). Another area of study is the use of abciximab in conjunction with carotid artery stenting, where the incidence of stroke and RIND tops 10%.

Conclusion

Successful inhibition of the glycoprotein IIb/IIIa receptor, most clearly shown in clinical trials of abciximab, enhances therapeutic outcomes in patients undergoing PTCA and may safely expedite care for patients with acute ischemic syndromes. Recently presented but not yet published results with other intravenous glycoprotein IIb/IIIa inhibitors will likely expand our therapeutic choices in this exciting class of antiplatelet agents. Oral agents may provide additional benefits from long-term treatment.

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