SMH ST. MICHAEL'S HOSPITAL
Cardiology
UNIVERSITY OF TORONTO

A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

XVIII™ CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY, AUGUST 25-29, 1996, BIRMINGHAM, UNITED KINGDOM

Improving the Outcome in Patients with Unstable Refractory Angina Undergoing PTCA: EPIC, EPILOG and the CAPTURE trials

Reported and discussed by: Anatoly Langer, MD

Plaque rupture and coronary thrombus formation is critical in the pathogenesis of acute ischemic syndromes. Despite successful pharmacologic therapy directed at thrombolysis, antithrombotic treatment remains suboptimal. In the attempt to improve upon the effectiveness of Aspirin as an antiplatelet drug, attention has been focused upon the glycoprotein IIb/IIIa receptor. This receptor is an integral part of the final common pathway of platelet aggregation which involves binding of fibrinogen and crosslinking of platelets.[1,2] While a number of glycoprotein IIb/IIIa receptor inhibitors have been studied, including a cyclic heptapeptide integrelin and the synthetic peptide-like molecules Lamifiban and Tirofiban, none have so far been shown as effective as a monoclonal antibody c7E3 also known as abciximab.

The antibody consists of a humanised murine monoclonal IgG molecule. After pilot studies confirmed safety and efficacy of this compound,[3,4] a number of large scale phase III clinical trials were undertaken. In addition to the question of how to improve the outcome of patients with unstable angina undergoing PTCA, there remains a very important question of how to decrease the rate of restenosis. After PTCA restenosis leads to recurrent symptoms and the need for repeat revascularization in more than 25% of patients within 6 months.[5,6] Because of the prevalence of PTCA in everyday practise, restenosis is associated with a significant financial burden, for example in the U.S. its cost is more than $2 billion per year.[7,8] The main cause of restenosis is vascular injury followed by platelet-rich thrombus formation and stimulation of smooth muscle cells to migration, secretion, and proliferation.[9-11] Until the results of clinical trials with abciximab became available, no other compound was shown to be effective in reducing restenosis in a large-scale clinical trial.

EPIC trial

Three recent trials (Figure 1) have studied administration of abciximab in various patient subgroups undergoing PTCA. EPIC trial[12,13] evaluated administration of abciximab in high risk patients. In 56 centers in the USA, 2,099 patients undergoing high risk PTCA were enrolled. The high risk patient population consisted of acute Q MI within 12 hours (3%), unstable angina or non-Q wave MI (23%), and other high risk patients including B_2 lesions and diabetes mellitus (73% of all enrolled patients).

All patients received once a day Aspirin 325 mg at least two hours before procedure, heparin bolus for a target ACT of 300-350 seconds, and heparin infusion for at least 12 hours after the procedure to maintain the PTT 1.5-2.5 control. In addition to the above therapy, patients were randomized to receive either placebo, abciximab bolus (0.25 mg/kg), or abciximab bolus (0.25 mg/kg) and infusion (0.01 mg/minute) for 12 hours starting 10 minutes before procedure.

Assessment of outcome at 30 days demonstrated significant benefit in the group receiving abciximab bolus and infusion (Table 1).

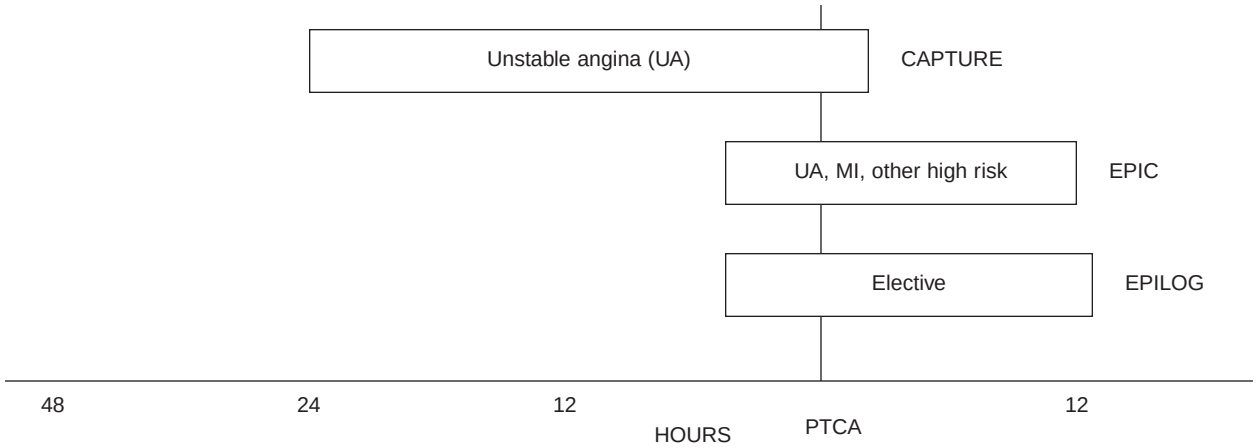
An improvement in outcome was associated with a significantly increased bleeding risk (Table 2).

Dr. A. Michael Lincoff from Cleveland, Ohio presenting these results identified administration of heparin as having possibly played a key role in increased bleeding risk.

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

The opinions expressed are only those of the Divisional members.
This publication is made possible through unrestricted grants.

Figure 1: Summary of Recent Trials with Abciximab



Assessment of outcomes in 6 months has demonstrated continuing benefit of abciximab administered as a bolus plus infusion (Table 3).

A number of important observations were pointed out during the presentation. The benefit observed in abciximab bolus plus infusion group beyond 48 hours was directly related to reduction of restenosis and, therefore, lesser need for repeat PTCA. This observation highlights the important difference associated with abciximab. Abciximab is a relatively non-specific inhibitor of IIb/IIIa receptor and also interacts and inhibits Vitronectin ($\alpha_v\beta_3$) receptor in the arterial wall, the stimulation of which has been found to play a key role in restenosis. Thus, other IIb/IIIa inhibitors, which have been shown to be specific for glycoprotein IIb/IIIa receptor, do not interact with Vitronectin and, therefore, may not have the same effect. These important, but not yet clearly proven observations require further testing.

It was also pointed out that inspection of Kaplan Meier curves over a period of the first 6 months and beyond suggests an incremental, or at least longlasting, benefit from administration of abciximab bolus and infusion. Preliminary results of a 3 year follow-up presented during the meeting suggested at least continuing benefit and possibly an increase in benefit in patients treated with abciximab bolus and infusion.

EPILOG study

The results of the EPILOG study were also presented for the first time by Dr. Lincoff. In EPILOG study, all patients undergoing PTCA were enrolled in 70 centers in Canada and US. Scheduled to enroll 4,800 patients referred for elective or urgent PTCA, not including patients with unstable angina, acute MI, or those undergoing atherectomy or at risk for excessive bleeding, the study was prematurely stopped with a final enrollment of 2,792 patients. All patients received Aspirin 325 mg a day and were randomized to standard dose heparin to achieve ACT ≥ 300 seconds, abciximab bolus (0.25 mg/kg) and infusion (0.01 mg/minute) for 12 hours in addition to standard dose heparin to achieve ACT ≥ 300 seconds, or abciximab bolus and infusion in addition to low dose heparin to achieve ACT ≥ 200 seconds.

Assessment of outcome at 30 days revealed significant reduction in composite end point of deaths, myocardial infarction, and urgent revascularization in both groups receiving abciximab with standard dose of heparin (5.4%) or low dose heparin (5.2%) by comparison to placebo (11.7%, $p < 0.01$). There was a significant, almost 50%, reduction in prevention of myocardial infarction in both abciximab groups by comparison to placebo. The relative benefit of abciximab administration was seen in all subgroups of patients, including 24% reduction combined end point in patients with recent (< 7 days) myocardial infarction, 63% reduction in patients with unstable angina, and 75% reduction in patients with stable angina. Absolutely no increased risk of bleeding was seen with administration of abciximab and, in fact, major bleeding was observed at its lowest rate in abciximab with low dose heparin (2%) by comparison to abciximab with standard dose of heparin (3.5%) or placebo (3.1%). There was also no difference in intracranial hemorrhage or any stroke.

Thus, comparison of EPILOG to EPIC study demonstrates significant benefit in patients with all ischemic syndromes undergoing PTCA with a significant improvement in safety, which is likely related to administration of weight adjusted and low dose heparin.

CAPTURE trial

The latest of these is the CAPTURE trial which was recently presented at the XVIIIth Congress of the European Society of Cardiology in the last week of August, 1996 in Birmingham, United Kingdom by Dr. Alec Vahanian from Paris, France. The CAPTURE Trial was performed in 69 centers in 12 countries and

was scheduled to include 1,400 patients with refractory angina of < 48 hours of duration who, following initial treatment with Aspirin, heparin, and nitrates would be randomized to abciximab bolus plus infusion vs placebo in addition to on-going treatment with heparin and Aspirin and within 24 hours of diagnostic coronary angiography in preparation for PTCA. The aim of the CAPTURE trial was to validate that the risk of complications during PTCA in patients with unstable and refractory angina would be reduced by treatment with abciximab.

At the third interim analysis and enrollment of 1,266 patients, the study was stopped prematurely on the advice of the Data Safety Monitoring Board. This decision was reached because there was a significant reduction in myocardial infarction in the abciximab group (12.1%) by comparison to placebo (8.2%, p = 0.002), as well as urgent intervention (7.8% vs 10.9%, p = 0.054). While no difference in mortality (1.0% vs 1.3%) was demonstrated, there was highly significant reduction at 30 days in the composite end point of death, MI, and urgent intervention (11.3% vs 15.9%, p = 0.002). The beneficial effect of reduction in myocardial infarction persisted to 6 months in abciximab by comparison to placebo (6.4% vs 8.9%, p < 0.05). There was, however, an increase in major bleeding which was significant (3.8% vs 1.9%, p = 0.043), however, no difference in strokes was observed.

Continuing reduction of myocardial infarction notwithstanding, assessment of outcomes at 6 months demonstrated no benefit with respect to mortality (2.1% vs 2.6%) or urgent intervention (25.9% vs 25.6%). When risk of urgent intervention at 6 months was further broken down, it became apparent that there was continuing benefit with respect to prevention of urgent CABG but not PTCA. These results, by comparison to the results of EPIC and EPILOG, suggest that duration of infusion is likely to be very important post PTCA (Figure 1). Basic data from Eli Lilly Laboratories suggest that activation of smooth muscle cells occurs in 12 hours post PTCA as a result of Vitronectin activation.

EPIC TRIAL 1991

Table 1: Outcomes at 30 days

	Placebo	Abciximab Bolus Only	Abciximab Bolus + Infusion	Relative Difference (%) Abciximab Bolus + Infusion vs Placebo	p Value
Death (%)	1.7	1.3	1.7	-	-
Q wave MI (%)	8.6	6.2	5.2	39.5	0.014
Urgent Intervention (%)	7.8	6.4	4.0	48.7	0.003
Composite end point	12.8	11.5	8.3	35.2	0.008

Table 2: Safety

	Placebo	Abciximab Bolus Only	Abciximab Bolus + Infusion	p Value
Major bleeding (%)	6.6%	11.1%	14.0%	0.001
Transfusion of RBC/whole blood	7.0%	13.2%	15.2%	0.001
Platelet transfusion (%)	2.6%	4.2%	5.5%	0.006

Table 3: Outcomes at 6 months

	Placebo	Abciximab Bolus Only	Abciximab Bolus + Infusion	Relative Difference (%) Abciximab Bolus + Infusion vs Placebo	p Value
Deaths (%)	3.4	2.6	3.1	9	0.834
MI (%)	10.5	8.0	6.9	34	0.018
PTCA(%)	20.9	19.7	14.4	31	0.001
CABG (%)	10.9	9.9	9.4	14	0.347
Composite end point	35.1	32.6	27.0	23	0.001

Conclusion

In conclusion, the results of EPIC, EPILOG and CAPTURE suggest that administration of abciximab as a glycoprotein IIb/IIIa platelet receptor inhibitor is associated with significant improvement in patient outcome. The benefit is observed in all patient subgroups and is related to the administration of abciximab at the time of PTCA. Abciximab administration should begin before PTCA and extend for 12 hours after. Further safety with respect to reduction of bleeding risk can be obtained through modification of heparin administration. Abciximab is a significant addition to our arm in treating patients with ischemic syndromes who are undergoing PTCA. Whether or not administration of abciximab, or other glycoprotein IIb/IIIa receptor inhibitors will result in diminished need for revascularization and improved outcome without PTCA, will be studied in a number of upcoming trials.

References

1. Plow EF, Ginsberg MH. Cellular adhesion: GP IIb/IIIa as a prototypic adhesion receptor. *Prog Hemostas Thromb* 1988;296:320-31.
2. Coller BS. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet GP IIb/IIIa complex. *J Clin Invest* 1985;76:101-08.
3. Ellis SG, Tcheng JT, Navetta FI, et al. Safety and antiplatelet effect of murine monoclonal antibody 7E3 Fab directed against platelet glycoprotein IIb/IIIa in patients undergoing elective coronary angioplasty. *Cor Art Dis* 1993;4:167-75.
4. Tcheng JE, Kleiman NS, Miller MJ, Sane DC, Wang AL, Weisman HF. Chimeric antiplatelet GP IIb/IIIa receptor antibody (c7E3) in elective PTCA: safety and platelet function inhibition. *Circulation* 1991;84(suppl II):II-590.
5. Popma J, Califf RM, Topol EJ. Clinical trials of restenosis after coronary angioplasty. *Circulation* 1991;84:1426-36.
6. Herrman JR, Hermans WRM, Vos J, Serruys PW. Pharmacological approaches to the prevention of restenosis following antioplasty. *Drugs* 1993;46:259-62.
7. Topol EJ, Ellis SG, Cosgrove DM, et al. Analysis of coronary angioplasty practice in the United States using a private insurance database. *Circulation* 1993;87:1489-97.
8. Hillegass WB, Ohman EM, Califf RM. Restenosis: the clinical issues. In: Topol EJ, ed. *Textbook of interventional cardiology*, 2nd ed. Philadelphia: Saunders, 1994:415-35.
9. Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. *J Am Coll Cardiol* 1991;17:758-69.
10. Ip JH, Fuster V, Israel D, Badimon L, Badimon J, Chesebro JH. The role of platelets, thrombin and hyperplasia in restenosis after coronary angioplasty. *J Am Coll Cardiol* 1991;17:77B-88B.
11. Casscells W. Migration of smooth muscle and endothelial cells: critical events in restenosis. *Circulation* 1993;86:723-29.
12. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high risk coronary angioplasty. *N Engl J Med* 1994;330:956-961.
13. EPIC Investigators. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa Integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994;343:881-86.