GP IIb/IIIa Blockers in PCI: Challenging the “Gold” Standard?
More Questions than Answers

The contemporary use of GP IIb/IIIa blockers in PCI continues to evolve as new evidence is demonstrated and ongoing trials near completion. However today, more questions arise than answers. Why did abciximab become the “gold” standard? Is there a pharmacologic difference in the GP IIb/IIIa blockers? Do unique pharmacologic characteristics translate into a durable clinical effect? Will eptifibatide’s short-term PCI benefits translate into a durable effect? Is tirofiban non-inferior to abciximab? What does non-inferior really mean? Will the TARGET trial prove anything meaningful? Will decreased costs outweigh the importance of clinical benefit? An assessment of today’s evidence and insights into ongoing trials is provided.

Since the original clinical trials demonstrated the benefit of platelet GP IIb/IIIa blockers in percutaneous coronary intervention (PCI) patients, there has been a substantial change in clinical practice with the adoption of stenting. Approximately 75% of the 650,000 patients that will undergo (PCI) in the U.S. within the next year will receive a coronary stent. However, this benefit must be balanced by the financial pressures in health-care systems today. Thus, the economics GP IIb/IIIa blockers in this setting are an important stimulus to considering therapeutic equivalence and defining an agent of choice. Ultimately, clinical evidence and patient outcomes must primarily guide therapy.

Abciximab: Establishing the Gold Standard

Although stents have favorably impacted the incidence of clinical restenosis and the need for repeat revascularization, the EPISTENT trial, which combined abciximab (0.25 mg/kg bolus, then 0.125 ug/kg/min infusion for 12 hours) with stenting, was the first controlled trial to demonstrate a durable reduction in death and myocardial infarction in these patients. The primary endpoint in the EPISTENT trial was a composite of death, myocardial infarction, or need for urgent revascularization in the first 30 days. Secondary endpoints included death or myocardial infarction at 6 months, target vessel revascularization at 6 months, and death at one year. The primary composite endpoint at 30 days occurred in 10.8% of 809 patients in the stent plus placebo group and 5.3% of 794 patients in the stent plus abciximab group (p<0.001). Major bleeding complications occurred in 2.2% of patients assigned stent plus abciximab vs. 1.5% assigned stent plus abciximab (p=0.38).

At 6 months, the composite endpoint of death and myocardial infarction in the stent plus abciximab arm was again reduced by approximately 50% compared with stent placement only. At one year, the composite endpoint in patients who received a stent plus abciximab therapy was still reduced by over 50% compared to stent placement only. In addition, mortality data at one-year demonstrated that for every 1,000 patients treated with a stent and abciximab, fourteen lives were saved as compared to stents alone (1.0% vs. 2.4%,
The approximate cost of abciximab in this scenario is $1,350 per patient.

The short-term benefits of eptifibatide and tirofiban in PCI were first evaluated in the IMPACT and RESTORE trials, respectively.\textsuperscript{3,4} Although questions have been raised about the doses of eptifibatide and tirofiban which were employed in these trials, neither agent produced a significant reduction in the primary composite endpoint of death, MI, or urgent revascularization at 30 days. However, eptifibatide was subsequently approved by the Food and Drug Administration (FDA) in PCI patients. The estimated cost for eptifibatide in this scenario is $150. Due to the lack of evidence, tirofiban is not labeled for PCI at this time. Considering the results of these early studies and the profound reduction in ischemic events and death rates in EPISTENT, abciximab in combination with stent placement was established as the standard of care in PCI patients.

**GP IIb/IIIa Pharmacologic Differentiation**

Although the short and long-term efficacy of abciximab in patients undergoing coronary stenting has been clearly demonstrated in the EPISTENT trial, it is unknown if the small molecule GP IIb/IIIa blockers (eptifibatide and tirofiban) are similar enough to abciximab, in terms of their pharmacologic characteristics and pharmacodynamic effects, to be as efficacious (short and long-term) in this setting. Although all three agents exert a potent effect in blocking GP IIb/IIIa integrin receptors on the surface of platelets, their pharmacologic and pharmacokinetic profiles differ significantly.

Recent studies have affirmed the importance of inflammation as a cause of plaque vulnerability, plaque rupture, and microembolization leading to ischemia at the tissue level. It is not yet known whether down-modulation of inflammation, which can be achieved with agents such as HMG Co-A reductase inhibitors, will improve the outcomes of these patients. Abciximab is the only GP IIb/IIIa blocker that has been shown to suppress this inflammatory process through white cell receptor blockade. In addition to blocking the GP IIb/IIIa integrin receptors on the platelet surface, abciximab remains unique in its ability to block the $\alpha_b$ integrin receptor (vitronectin receptor) within the endothelium. It is postulated that blockade of these receptors suppresses smooth muscle cell proliferation and may partially explain the drug's durable clinical benefit.

Also, “passivation” of coronary arteries has been demonstrated in studies such as the EPILOG and EPISTENT trials where abciximab was employed.\textsuperscript{1,2,5} Passivation in this context means that the GP IIb/IIIa blocker exerts multiple effects within the vessel and endothelium such that the vascular surface is no longer able to support the propagation of thrombus. It has been further postulated that some of the clinical benefit of abciximab may be independent of the potent periprocedural antiplatelet action and related to its anti-inflammatory actions and $\alpha_b$ integrin receptor (vitronectin) blockade. Eptifibatide and tirofiban have not been postulated to exert these pharmacologic actions nor do they have the same pharmacokinetic characteristics in terms of duration of action.

**ESPRIT: Will 48-Hour Results Translate into a Durable Effect?**

The ESPRIT and TARGET trials were undertaken to answer the question: even though the pharmacologic profiles of the smaller molecule GP IIb/IIIa blockers (eptifibatide and tirofiban) are different than abciximab's, can they produce short and long-term outcomes in PCI patients that undergo stenting? The efficacy of eptifibatide vs. placebo in patients undergoing stent implantation was investigated in the Enhanced Suppression of Platelet Glycoprotein IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) study. This trial was originally designed to enroll 2,400 patients on an intent to stent basis. Patients were randomized to either placebo, or eptifibatide 180-ug/kg bolus with a repeat bolus 10 minutes later, with a constant 2.0 ug/kg/min infusion for 12 hours. The primary endpoint of the study was the composite incidence of death/MI/urgent revascularization or bailout at 48 hours. The trial was terminated prematurely at the recommendation of the Data Safety Monitoring Board (DSMB) at an interim analysis after a total of 2,064 patients had been enrolled in the trial.

As presented by Dr. James Tcheng at the American College of Cardiology meeting in Anaheim (March 2000), at 48 hours there was a significant reduction of the primary composite endpoint, 6.6% in the eptifibatide group, versus 10.5% in the placebo group (a relative reduction of 37%, $p<0.01$). At 30 days, there again was a significant reduction of the primary composite endpoint, 7.5% in the eptifibatide group, versus 11.7% in the placebo group (a relative reduction of 36%, $p<0.01$). There were no significant differences between the groups in terms of major bleeding. In contrast to eptifibatide, abciximab reduced short-term ischemic events in EPISTENT by about 50%. The question remains regarding the comparability of results from these trials.

The long-term results of ESPRIT are still awaited. The durability of the clinical benefit, particularly out to 6 months and 1 year, has yet to be determined. It also remains to be seen whether there will be a mortality benefit at one year as has already been demonstrated with abciximab in the EPISTENT trial. Once we possess this long-term outcome data, we will be better positioned to determine if eptifibatide may be considered as a durable alternative to abciximab in the catheterization laboratory.
If this is indeed demonstrated, then economics will become an even more important factor in product selection.

TARGET: No Surprises Expected from this Non-Inferiority Trial

The clinical community has long awaited a head-to-head trial of GP IIb/IIIa blockers in the setting of PCI. The relative efficacy and safety of abciximab and tirofiban was compared in the Do Tirofiban and Abciximab for Revascularization Give Equivalent Outcomes? (TARGET) trial. TARGET was a randomized, double-blind, head-to-head trial comparing abciximab and tirofiban in 4,750 patients undergoing coronary intervention. The primary endpoint was the composite incidence of death, MI, and urgent TVR at 30 days. The dose of tirofiban in TARGET was a modified version of the RESTORE trial dosing regimen: a bolus of 10 µg/kg over 3 minutes followed by an infusion of 0.15 µg/kg/minute for 18-24 hours. The trial was powered to assess "non-inferiority"; that is, it is designed as a non-inferiority trial to demonstrate that tirofiban is not inferior to or not substantially worse than abciximab. Non-inferiority is a relatively new term that has not been universally adopted. Although both non-inferiority and equivalence trials have been referred to as "equivalence" trials, there is an important distinction between them. Equivalence trials attempt to show that the clinical effects differ by no more than a specific amount. This tolerance is known as the equivalence margin. In an equivalence trial, if the clinical effects of the two treatments differ by more than the equivalence margin in either direction, then equivalence has not been shown. Non-inferiority trials, on the other hand, attempt to show that an experimental treatment is not worse than an active control by more than the pre-specified margin. Inherent problems with non-inferiority trials such as difficulty in specifying an appropriate non-inferiority margin make their results clearly less credible than those of a placebo controlled trial.

The definition of non-inferiority in the TARGET trial is very broad. As a non-inferiority trial, the TARGET trial allows the comparator drug (tirofiban) a wider margin of variance and still conclude that the effects of the drug are adequate to meet the predetermined clinical demands. For example, if the abciximab event rate in TARGET is the same as in EPISTENT, at 5.3%, non-inferiority will be declared if the tirofiban event rate is up to 6.2%. This calculates to a maximum odds ratio of 1.18 with an upper 95% confidence interval of 1.46. This implies that as long as the confidence interval line does not cross 1.46, the tirofiban treatment arm can be 18% worse than the abciximab arm and still achieve the study goal of non-inferiority.

For a non-inferiority trial such as TARGET, one has to decide if the "maximum boundaries" and statistical assumptions will be accepted by the clinical community as providing a similar or acceptable level of clinical efficacy. The comparator drug (tirofiban) must preserve most of the benefit that the accepted drug (abciximab) achieves. Does TARGET answer the question: Is tirofiban as good as abciximab in stented patients? Although the trial is directed at the question, it answers it relatively, only according to how "as good as" is defined by the study. Thus, although the trial is a head-to-head comparison of two active agents in the same population, at the same time it says that tirofiban will be judged to be non-inferior to abciximab if it is up to 47% inferior to abciximab.

Conclusion: Challenging the Gold Standard

Several of the key questions pertaining to the use of GP IIb/IIIa blockers in PCI have been addressed. Why did abciximab become the "gold" standard? The short and long-term results of the EPILOG and EPISTENT trials originally established abciximab as the standard of care in PCI. Is there a pharmacologic difference in the GP IIb/IIIa blockers? As discussed, there are clear differences in the pharmacologic and pharmacokinetic profiles of the GP IIb/IIIa blockers. Do unique pharmacologic characteristics translate into a durable clinical effect? The unique characteristics of abciximab have translated into both a short-term and durable benefit.

Several questions remain unanswered. Will eptifibatide's short-term PCI benefits translate into a durable effect? Is tirofiban non-inferior to abciximab? What does non-inferior really mean? Will the TARGET trial prove anything meaningful? Will decreased costs outweigh the importance of clinical benefit?

Other practical questions arise. First, will the clinical community ever fully understand the trial design, "maximum boundaries", and statistical assumptions of the TARGET trial? It is likely that the entire clinical community will be confused by this trial and that the design, assumptions, and results will not be fully understood. Will the clinical community accept the potential for a reduced level of clinical efficacy with tirofiban? There will likely be significant concern about accepting a drug with reduced efficacy even if it is shown to be "non-inferior".

Unquestionably, we will gain valuable insight into the issue of equivalence between GP IIb/IIIa blockers in PCI/stent patients as these key questions are answered and long-term benefit of eptifibatide and tirofiban are determined. Until then, the published evidence and durability of effect should guide clinical decisions regarding the agent of choice in PCI. However, current standards must continually be challenged and progress in the management of PCI must be pursued.

References

GUSTO IV ACS: Lack of GP IIb/IIIa Benefit in UA Medical Stabilization?

Unstable angina (UA) and non-ST segment elevation acute coronary syndrome (ACS) patients are generally treated in one of two ways: early conservative medical therapy or early percutaneous coronary intervention (PCI) therapy. Many patients undergoing early PCI today receive abciximab therapy because dramatic improvements in both short-term and long-term outcomes have been demonstrated (EPISTENT). More recently, eptifibatide (ESPRIT) has been shown to improve short-term outcomes in PCI, however, long-term results are awaited. Patients who are unresponsive to conventional medical therapy and are scheduled to undergo PCI within 24 hours are candidates for abciximab therapy (CAPTURE). Until GUSTO IV ACS, abciximab has not been studied as pure medical therapy in patients in whom PCI was not planned. GUSTO IV ACS evaluated the safety and efficacy of abciximab given as first line medical therapy in a broad population of patients with UA or non-ST elevation ACS specifically where PCI was not planned.

GUSTO IC ACS was a multinational, multicenter, randomized, double blind, placebo-controlled trial in patients with ACS without ST-segment elevation. The primary hypothesis was that both 24- and 48-hour infusions of abciximab when compared to placebo (aspirin and heparin alone) would reduce the composite endpoint of death of MI at 30 days. GUSTO IV ACS was to answer several other key questions. What is the best dosing regimen to use in this setting? Is it safe to combine abciximab with a low molecular weight heparin? Is troponin the best marker of which patients will benefit most?

The trial randomized 7,800 patients believed to have UA to three different groups - placebo, abciximab bolus plus 24-hour infusion, or abciximab bolus plus 48-hour infusion. The abciximab bolus was 0.25 mg/kg, which is the same as has been used in previous trials. The abciximab infusion was administered at 0.125 µg/kg/min to a maximum of 10 µg/min.

Both abciximab doses were larger than those used in the PCI setting, where the infusion is given for just 12 hours. Once again, the trial was designed to test the drug in the absence of interventions, and only 1.6% of patients underwent revascularizations during the treatment period. This is a major difference from other trials of GP IIb/IIIa blockers in unstable angina.

Data presented at the European Society of Cardiology Meeting in August of 2000 suggests the primary endpoint of death and myocardial infarction at 30 days was not significantly different between the three groups. In addition, abciximab did not show statistically better results in the subgroup of patients with raised troponin levels. Until now, raised troponin levels were believed to be one of the most reliable markers of coronary disease, but these results have also thrown that into question. The high proportion of women in the trial may be one possible explanation for this; women may show raised troponin levels without having true coronary disease.

The fact that abciximab did not demonstrate statistical benefit in UA and non-ST segment elevation ACS, is not well understood. There are many possible explanations including: a different patient population in the GUSTO IV ACS compared with the other unstable angina trials and concerns that in retrospect many patients may not have had true coronary disease; fewer interventions were performed than in other trials and that in those other trials there was also little benefit at 30 days in patients who had not had an early intervention; uncertainty over the dosing regimen used, with the possibility that prolonged platelet inhibition may have an untoward effect; and the possibility that the trial was underpowered as the event rate was lower than expected.

Several other previous trials have shown marginal benefit of other GP IIb/IIIa blockers in UA, namely PRISM Plus with tirofiban and PURSUIT with eptifibatide. Tirofiban did not produce statistically significant improvements at 30 days while eptifibatide did not produce statistically significant results at 6 months. The Prism Plus and Pursuit trials were conducted before eptifibatide and tirofiban were approved for any indication and thus they included some patients with PCI. In these trials, 10-20% of patients had PCI during administration of study drug, versus 1.6% in GUSTO IV ACS. Some have suggested that the results of eptifibatide and tirofiban in the setting of medical stabilization of UA (non-PCI patients) may actually be comparable to the results produced by abciximab. GP IIb/IIIa blockers may still have a role in UA patients who are at high-risk with angiographically proven disease and are not undergoing PCI.

References