ESPRIT in context: pharmacology matters!

One of the most notable advances in cardiology of the past decade has been the development and clinical application of a novel class of potent antiplatelet agents — the platelet glycoprotein (GP) IIb/IIIa integrin inhibitors. In the mid-1990s, large-scale, randomized, controlled clinical trials of these agents documented highly significant and clinically relevant reductions in the morbidity and mortality of percutaneous coronary intervention[1–5]. Subsequently, GP IIb/IIIa inhibitors were found to prevent ischaemic events in patients admitted with the acute coronary syndromes of unstable angina or non-Q wave myocardial infarction[6,7].

The first GP IIb/IIIa agent brought to market in the U.S.A. (1994) was abciximab (ReoPro, Centocor, Malvern, PA, U.S.A., and Eli Lilly, Indianapolis, IN, U.S.A.). Abciximab is the Fab fragment of a chimeric murine–human monoclonal antibody to the GP IIb/IIIa integrin. Abciximab binds to GP IIb/IIIa with high affinity and has a slow receptor off-rate, resulting in a long biological half-life (~12 h). In clinical trials, treatment with abciximab during percutaneous coronary intervention consistently provided impressive reductions in the incidence of ischaemic events across a series of trials including EPIC, EPILOG, CAPTURE, and EPISTENT[6,9]. In 1998, eptifibatide (Integrilin, COR Therapeutics, South San Francisco, CA, U.S.A., and Schering-Plough, Kenilworth, NJ, U.S.A.) and tirofiban (Aggrastat, Merck, West Point, PA, U.S.A.) were approved for use by the U.S.A. Food and Drug Administration. These agents are distinguished from abciximab by a much shorter half-life (~2–3 h), a rapid off-rate, and greater selectivity for the GP IIb/IIIa receptor complex. Results of pivotal clinical trials of these two agents in the percutaneous coronary intervention indication, however, were disappointing[4,5]. In the IMPACT II trial of eptifibatide and the RESTORE trial of tirofiban, lower degrees of absolute and relative benefit were seen in comparison to abciximab across a series of trials[10]. Potential explanations for this disparity included both pharmacodynamic issues (particularly the extended duration of action of abciximab) and the potential role of receptor cross-reactivity of abciximab with other receptors beside GP IIb/IIIa. Based on the trial results, the clinical and commercial consequences were to relegate eptifibatide and tirofiban to minimal levels of use in the percutaneous coronary intervention indication.

Other factors led concurrently to relatively low rates (~25% or less) of utilization of even abciximab in the percutaneous coronary intervention indication. Predominant among these was the cost of abciximab; at $1500 US per treatment, the cost was felt to justify prospective use (as evaluated in the respective clinical trials) in only the highest risk patients. Questions were raised also by the lack of reproducibility of effect in the small molecule trials as to whether or not the results seen with abciximab were truly robust.

The recent ESPRIT trial addressed these and other concerns directly[10]. In designing the ESPRIT study, an alternative explanation for the efficacy differences between abciximab and the small molecule inhibitors of GP IIb/IIIa was entertained. Specifically, it was theorized that the marginal efficacy results of the IMPACT II trial were due to dosing regimens of eptifibatide that provided only ~50–60% inhibition of platelet aggregation[11]. The initial bolus of abciximab is known to saturate available GP IIb/IIIa receptors, producing a high grade (>80%) of inhibition within minutes after administration[12]. Simulations of eptifibatide dosing suggested that substantially higher concentrations of drug (than had been used in IMPACT II) would be needed to saturate the receptor and maintain platelet inhibition. Using known pharmacokinetic parameters, this modelling also demonstrated a decrease in drug levels within the first hour after administration of a single bolus plus infusion. These simulations were confirmed in clinical studies[13]. Administration of additional drug (as a second bolus) early in the course of percutaneous coronary intervention appeared to be necessary to recapitulate the pharmacodynamic effects of abciximab. Therefore, a regimen of eptifibatide incorporating a double-bolus plus infusion regimen was developed for the ESPRIT study. This 'front-loaded' regimen provides a high degree of blockade of platelet aggregation particularly during the early peri-procedural period (analogous to the lidocaine multiple-bolus effect). Furthermore, this was accomplished at a cost of treatment of only $400 US.
Results of ESPRIT documented a 37% relative risk reduction (10.5% to 6.6%, \( P=0.0015 \)) in the primary composite end-point of death, myocardial infarction, need for urgent target vessel revascularization, and crossover to GP IIb/IIIa inhibitor therapy for thrombosis within 48 h. At 30 days, a 35% relative risk reduction (10 to 6.8%, \( P=0.0034 \)) in the key secondary end-point of death, myocardial infarction, and urgent target vessel revascularization was observed. This was accomplished despite the treatment of all patients with a thienopyridine (97% received clopidogrel) and allowance of crossover to open-label ‘bailout’ GP IIb/IIIa treatment in the placebo group. The bailout crossover control (where treatment is reserved for those developing an actual complication) was permitted as this best mimics actual practice. The ESPRIT study thus marks the first trial in which a small molecule inhibitor of GP IIb/IIIa achieved a treatment benefit on a par with that seen with abciximab. Secondary analyses documented robustness and consistency across each of the components of the end-point. Furthermore, substudy analyses showed that eptifibatide provided measurable benefits in improving microvascular perfusion, suggesting a mechanism for benefit independent of the prevention of thrombosis of epicardial vessels.\(^\text{[14]}\)

In addition to the overall treatment benefit, eptifibatide was associated with a lower incidence of clinical events in virtually every subgroup examined. While greater absolute benefits were seen in the highest risk subgroups, multivariable regression modelling did not identify a group of patients where benefit was not conferred.\(^\text{[15]}\) This included demographic factors such as gender, age, ethnicity and weight, as well as disease specific factors such as indication for the procedure (i.e. recent myocardial infarction, unstable angina, stable angina) and cardiovascular risk factors (diabetes, hypertension, hyperlipidaemia and history of tobacco use). Also, benefit was observed with the unrestricted use of contemporary stent designs and concomitant pharmacological therapy in treating a wide variety of lesions. In other words, despite the major strides in improving stent technology and technique, these data demonstrate the continued efficacy of GP IIb/IIIa blockade in contemporary percutaneous coronary intervention practice.

A final test of any therapeutic is durability. The 6 month follow-up programme in ESPRIT has now been completed, and a 35% relative risk reduction was documented in the key 6 month secondary end-point of death and myocardial infarction (11.5% vs 7.5%, \( P=0.0015 \)). Again, other combinations and permutations of this end-point and the end-point of death, myocardial infarction, and all target vessel revascularization consistently showed benefit with treatment compared to placebo, with benefit continuing to accrue between 30 days and 6 months (well beyond the period of treatment).

The ESPRIT study would appear to have settled the argument as to whether small molecule, short-acting, inhibitors of platelet GP IIb/IIIa can achieve robust and clinically important reductions in ischaemic clinical events that occur as a result of percutaneous coronary intervention. The fact that this can be achieved with an agent specific for GP IIb/IIIa focuses attention on the particular pharmacodynamics of platelet inhibition (rather than the agent used) as the focus of this class of therapeutics. The strategy of intense inhibition begun just before the percutaneous coronary intervention procedure and maintained throughout the infusion, especially in the early hours immediately following percutaneous coronary intervention, appears to have contributed to the successful outcome of this study. This approach proved superior to a ‘watchful waiting’ or ‘bailout’ strategy where treatment is reserved for those patients actually manifesting an angiographic complication. The favourable economics of eptifibatide, coupled with the robust early and long-term effects, argue strongly for the interventional community to consider pre-treatment as a standard of care for most if not all patients undergoing contemporary percutaneous coronary intervention.

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References:


