

Transitioning to Generic Clopidogrel

As antiplatelet therapy enters a transitional phase to generic clopidogrel, will this change drive more patient-tailored treatment?

BY PAUL A. GURBEL, MD

Since the FDA approved clopidogrel in 1997, this antiplatelet agent has revolutionized interventional cardiology and transformed therapy for non-STEMI, STEMI, and PCI-treated patients. Clopidogrel enjoyed a remarkable 15-year “home run” marketed under the name Plavix (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, NY), amassing tens of billions of dollars in sales and serving an estimated 115 million patients internationally and 50 million patients in the United States alone. The evolution continues with the expiration of the Plavix patent last month coupled with the FDA’s swift approval of generic forms of both the 75-mg daily dose and the 300-mg loading dose of clopidogrel.

One of the largest barriers to patient compliance and long-term therapy with branded clopidogrel was cost. Generic versions should substantially lower that barrier and may improve compliance and patient outcomes, especially in uninsured populations.

CONFIRMING ANTIPLATELET RESPONSE REMAINS CRITICAL

Clinicians need to be cautious to avoid allowing cost to be the most important factor in selecting a treatment option. Patients taking generic clopidogrel face the same pharmacodynamic limitations as with Plavix. In 2003, we first reported the unpredictable antiplatelet response to Plavix therapy and the important fact that approximately 30% of the PCI population had a negligible or absent pharmacodynamic effect.¹ This report was initially met with disbelief and opposition by many thought leaders. However, these findings have now been validated in thousands of patients studied internationally.

The unpredictable and, in some cases, absent pharmacodynamic effect following clopidogrel therapy laid the groundwork for the development new P2Y₁₂ inhibi-

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tors having more predictable pharmacodynamic profiles. In 2005, the important relation of high on-treatment platelet reactivity (HPR) to poststenting ischemic risk was reported in the single-center PREPARE POST-STENTING study.² Since then, numerous observational studies involving thousands of patients worldwide have confirmed the seminal findings of PREPARE POST-STENTING.³

Finally, in 2010, the first genome-wide association study identified a sole single nucleotide polymorphism associated with clopidogrel response variability. This single nucleotide polymorphism is CYP2C19*2. In the same publication, we reported the results of a validation study clearly demonstrating the increased risk of poststenting ischemic event occurrence in CYP2C19*2 carriers.⁴ The roles of genetic and platelet function testing in clinical practice are now addressed in the most recent American and European treatment guidelines. Thus, in the last 15 years, important strides have been made in understanding the role of genetics, drug-drug interactions, and many other factors influencing clopidogrel metabolism and its pharmacodynamic effect. A strong relation has now been established between HPR and poststenting ischemic event occurrence.

Arguably, P2Y₁₂ blockade is the most important and potentially life-saving pharmacologic strategy that we can provide to a stent patient. However, it may be risky to prescribe generic clopidogrel to patients without confirming an adequate pharmacodynamic response. Direct confirmation is provided by platelet function

testing, whereas genetic testing provides indirect evidence of an adequate response.

Payers are now more apt to demand this type of testing as well. Some progressive insurers are already requiring testing to determine the suitability of patients for the more expensive new P2Y₁₂ inhibitors, prasugrel (Effient, Daiichi Sankyo Company, Limited, Parsippany, NJ; Eli Lilly and Company, Indianapolis, IN) and ticagrelor (Brilinta, AstraZeneca Pharmaceuticals LP, Wilmington, DE).

Various companies are leading the way in point-of-care platelet function testing. With a defined HPR cut-point in place and recommendations in the guidelines, more cardiologists are now confirming the response to clopidogrel rather than relying on blind faith. Exciting preliminary evidence suggests that there may be a therapeutic window for P2Y₁₂ inhibition.⁵

With regard to the role of genetic testing in the PCI-treated patient, the presence of a homozygote for a loss-of-function allele should be a strong indication to use an alternative P2Y₁₂ inhibitor to clopidogrel. Similarly, a heterozygote for the loss-of-function allele may undergo platelet function testing to confirm the adequacy of the response to clopidogrel, and if inadequate, an alternative P2Y₁₂ inhibitor can be considered. Platelet function testing in clopidogrel-treated patients should allow for a maximal pharmacodynamic effect to occur. Therefore, 5 days of maintenance therapy, or at least 8 hours after an initial loading dose, would be suitable times to test, and this strategy has been employed in most investigations.

The role of follow-up testing is unresolved and understudied. Essentially, all of the major published data linking platelet function to post-PCI event occurrence has been based on one measurement of platelet function performed in-hospital after allowance for an adequate steady state pharmacodynamic effect to occur. The introduction of generic clopidogrel to the market could be a catalyst that drives clinicians to embrace platelet function testing and genotyping and potentially provide improved patient care while at the same time cutting cost.

BUYER BEWARE: QUESTIONS REMAIN REGARDING RELIABILITY AND SAFETY

It is vital to remember that the pharmacodynamic response, safety, and efficacy of the generic versions of clopidogrel have not been vetted in clinical trials. There are potentially serious issues that have yet to be completely examined and studied. The lack of longitudinal data on these generic medicines is sobering. The reliability of generic clopidogrel has not been tested, and there

could be variations in potency and consistency from batch to batch. Concerns have also been raised about the purity of generics after some clopidogrel pills manufactured in India were proven to contain significant levels of methyl chloride, a known carcinogen.⁶

MORE PREDICTABLE TREATMENT OPTIONS ARE AVAILABLE

Although clopidogrel will likely remain the most popular nonaspirin antiplatelet agent, the new P2Y₁₂ inhibitors, particularly prasugrel, continue to gain market share. Ticagrelor and prasugrel have more predictable and potent pharmacodynamic profiles and a more rapid onset of action than clopidogrel. These pharmacodynamic advantages have translated to fewer ischemic event occurrences but more bleeding in acute coronary syndrome patients who were studied in two large-scale trials. For the interventional cardiologist, a reduction in stent thrombosis is particularly notable.

Clinicians should strive to find an antiplatelet therapy that achieves the optimal level of platelet inhibition for the patient, regardless of cost. If generic clopidogrel is indeed pharmacodynamically effective in the patient, offering them this less-expensive option appears to be a win/win. The introduction of generic clopidogrel holds the strong possibility of inducing a change in practice whereby genetic and platelet function testing are performed more frequently in patients receiving a stent. This will allow the patient's platelet physiology to decide the course of treatment instead of the price tag on the pill bottle. ■

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