Emerging Antiplatelet Therapies in Percutaneous Coronary Intervention: A Focus on Prasugrel

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ABSTRACT

Background: Prasugrel is the most recent addition to the available thienopyridine antiplatelet agents used to prevent ischemic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention.

Objective: The aim of this article was to review published data on the efficacy and safety profile of prasugrel, cost considerations with its use, and its place in clinical care.

Methods: We searched PubMed and Ovid databases for English language clinical trial articles, published through December 2010, involving the use of prasugrel in human subjects. The key word *prasugrel* was used. The review focused on clinical trials, but other articles and Food and Drug Administration documents were also reviewed for relevant information.

Results: Phase II studies showed that prasugrel had a more powerful antiplatelet effect and was more effective in its inhibition of platelet activation than clopidogrel. In the only Phase III trial completed before its Food and Drug Administration approval, prasugrel demonstrated a decrease in the primary composite efficacy end point of the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke relative to clopidogrel (643 [9.9%] vs 781 [12.1%], respectively; $P = 0.001$). Prasugrel was associated with a significantly higher risk of bleeding compared with clopidogrel. Non–coronary artery bypass graft-related thrombolysis in myocardial infarction (TIMI) major bleeding occurred in 146 (2.4%) patients in the prasugrel group versus 111 (1.8%) patients in the clopidogrel group ($P = 0.03$). For every 1000 patients treated with prasugrel instead of clopidogrel, a total of 23 myocardial infarctions could be prevented at the cost of 6 additional TIMI major bleeding events. However, this benefit was diminished with longer-term therapy. Adverse outcomes of prasugrel use outweighed its benefits in certain subgroups, including patients >75 years old, those weighing <60 kg, and patients with a history of stroke or transient ischemic attack.

Conclusions: Prasugrel's clinical benefits were counterbalanced by an increase in bleeding risk compared with conventional thienopyridine treatment with clopidogrel. Current practice guidelines incorporated prasugrel as a treatment option, but at this time do not recommend that prasugrel be selected over clopidogrel in any patient subgroup. Further study is required to determine optimal dosing and proper patient selection with prasugrel treatment. (*Clin Ther*. 2011;33: 425–442)

Key words: ACS, antiplatelet, clopidogrel, PCI, prasugrel, thienopyridine.

INTRODUCTION

Prasugrel is a third-generation thienopyridine antiplatelet agent that was approved by the US Food and Drug Administration (FDA) on July 10, 2009, for use in patients with acute coronary syndrome (ACS) who were undergoing percutaneous coronary intervention

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(PCI).[1] Current standard treatment for the prevention of thrombosis after PCI in ACS patients is dual antiplatelet therapy with aspirin and a thienopyridine.[1] The currently approved thienopyridine agents include ticlopidine, clopidogrel, and prasugrel. Initial trials that supported thienopyridine use in PCI involved ticlopidine.[2] Use of ticlopidine had largely been replaced by clopidogrel at the time of the Phase II prasugrel trials, owing to clopidogrel's once daily dosing schedule and its lower incidence of neutropenia relative to ticlopidine (0% vs 0.3%; *P* value not given).[3,4] Over the past decade, dual antiplatelet therapy with aspirin plus clopidogrel became the standard of care after ACS and PCI.[5–7] However, recent studies found that high on-treatment platelet reactivity (HTPR) was linked to increased atherothrombotic events and that genetic polymorphisms could affect patient response to antiplatelet treatment with clopidogrel.[8–10] Thus, a need existed for newer agents with less variable antiplatelet activity. Bleeding risk with antiplatelet treatment was also a concern that had to be balanced with the selected agent's efficacy.

The addition of prasugrel to the available armamentarium of antiplatelet agents yielded another pharmacologic option for management of patients with ACS who underwent PCI. Shortly after the FDA approval of prasugrel, the American Heart Association and the American College of Cardiology released a focused update on their ST-segment elevation myocardial infarction (STEMI) and PCI guidelines to include this newest agent, yet many questions remained on the actual place in therapy of this agent[5] (see **Table I** for a summary of this update).[11–16] Thus, clinical guidance was needed for the appropriate use of prasugrel and determination of its role in therapy. This article reviewed available clinical data and highlighted practical considerations regarding prasugrel's implementation and use in clinical practice.

METHODS

The literature was reviewed through December 2010 using the key word *prasugrel* for publications in the National Library of Medicine's PubMed database. No lower date limit was set. As of December 29, 2010, the search resulted in 409 papers from PubMed. The search resulted in 51 English reports of human participants in clinical trials. The prasugrel key word search identified 349 papers in Ovid MEDLINE. Limits set in the search resulted in 262 English-language human participants articles, 63 of which were in core clinical journals. The principal inclusion criterion was a design of randomized controlled trial. Reference lists of the selected articles and guidelines were also reviewed for additional information. Review articles and letters were reviewed for relevant information. The clinical trials database (clinicaltrials.gov) and FDA preapproval documents were also reviewed. In vitro/ex vivo or animal studies were not included in the initial review but were evaluated for pharmacodynamic and pharmacokinetic data supplementation.

PHARMACOLOGY, PHARMACOGENOMICS, AND DRUG INTERACTIONS

Thienopyridines are prodrugs whose active metabolites inhibit platelet aggregation and activation by irreversibly antagonizing the $P2Y_{12}$ adenosine diphosphate receptor on the surface of platelets. Prasugrel is extensively metabolized and rapidly absorbed; its maximum plasma concentration is reached in 30 minutes.[17] Prasugrel is hydrolyzed by esterases to an intermediate compound, then oxidized by cytochrome P-450 (CYP) to its active metabolite, R-138727. The main contributors to its metabolism are CYP2B6 and CYP3A4, and smaller contributions result from CYP2C9 and CYP2C19.[18,19] Moderate hepatic impairment did not necessitate prasugrel dose adjustment, as it did not affect platelet aggregation or metabolite production in prasugrel-treated patients compared with controls[20] (see **Table II** for a comparison of prasugrel and clopidogrel characteristics).[8,9,15,17–32]

Clopidogrel is largely (~85%–90%) hydrolyzed via esterases to terminal inactive metabolites, and the unhydrolyzed portion is metabolized with 2 CYP-450 steps (including CYP2C19) to form its active metabolite. Clopidogrel has variable pharmacodynamics and pharmacokinetics. It has a slower speed of onset with a 300-mg loading dose compared with a 60-mg loading dose of prasugrel (23% decrease in maximum platelet aggregation [MPA] per hour vs 203% decrease in MPA per hour respectively; $P < 0.001$).[21] Variability in MPA among patients at >1 hour after administration was less for prasugrel than for clopidogrel ($P < 0.001$).[21] Prasugrel achieved a more potent antiplatelet effect, as measured via inhibition of platelet aggregation (IPA) at 30 minutes after a 60-mg loading dose versus clopidogrel at loading doses of 300 and 600 mg (54% vs 3% and 6%, respectively; $P < 0.001$).[22] Prasugrel's IPA at 30 minutes after a 60-mg loading dose