Advance reports

Included in this report are the highlights of the American Heart Association's Scientific Sessions from Orlando and also the American Society for Oncology (ASCO) Genitourinary (GU) Cancers Symposium in San Francisco, California.

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PONI Q192R genetic variant and response to clopidogrel and prasugrel

Clopidogrel and prasugrel are pro-drugs requiring biotransformation into active metabolites. Multiple studies have validated the relationship between loss-of-function alleles in the CYP2C19 gene and the pharmacological and clinical response to clopidogrel. Recently, a study has proposed that a functional genetic variant (Q192R, rs662) in the paraoxonase gene (PON1) significantly enhances the biotransformation of clopidogrel.

In further data presented at the American Heart Association (AHA) 2011 Scientific Sessions, Orlando, Florida, PON1 rs662 was genotyped in 275 healthy subjects treated with clopidogrel or prasugrel. The association with plasma concentrations of active drug metabolites and change in maximal platelet aggregation was tested. A separate cohort of 3,000 patients with an ACS treated with clopidogrel or prasugrel in the TRITON-TIMI 38 trial were also genotyped.

It found that in healthy subjects, there were no significant associations between rs662 and plasma concentrations of active drug metabolite (p=0.62) or change in platelet aggregation (p=0.51) for loading or maintenance dosing. Likewise, among prasugrel-treated subjects, there were no significant associations between rs662 and plasma concentrations of active drug metabolite (p=0.88) or change in platelet aggregation (p=0.97) for loading or maintenance dosing.

It concluded that in contrast to prior observations, in the present study, the Q192R (rs662) genetic variant in PON1 was not associated with the pharmacological response to clopidogrel, nor was it associated with the response to prasugrel.

1 Mega J et al. Abstract 11255: PON1 Q192R (rs662) Genetic Variant and Response to Clopidogrel and Prasugrel. American Heart Association (AHA) 2011 Scientific Sessions, Orlando, Florida

Study sponsored by Daiichi Sankyo

Prasugrel treatment is more effective in reducing platelet reactivity in PCI patients

Prasugrel is significantly more effective in achieving sufficient platelet inhibition in low responders to the standard clopidogrel-dose compared to a dose increase of clopidogrel dose according to data also presented at the AHA.

There was a reduction of the average aggregation by 54% versus 31% for clopidogrel. The effect is achieved at the cost of an increased higher response rate which has been shown to be associated with more major bleeding.

A dual anti-platelet therapy is a routine procedure after percutaneous coronary intervention (PCI). A low response to thienopyridine treatment (LR) as determined by platelet function testing has been shown to be associated with a significantly increased risk for stent thrombosis and other ischaemic events. In order to intensify the anti-platelet regimen patients can either be reloaded with clopidogrel with the subsequent increase of its daily dose to 150mg/d or the treatment can be switched to prasugrel.

Platelet function testing using multiple electrode aggregometry was performed in 1028 patients undergoing PCI. Patients with low response to initial clopidogrel loading dose (600mg) and treatment (75mg) were either reloaded with 600mg clopidogrel and then treated with daily 150mg clopidogrel (Group I, n=64) or were immediately switched to prasugrel loading dose (60mg) and standard daily therapy (10mg) (Group II, n=40). The

platelet function was retrospectively analysed in both groups.

1. Schmidtler F, et al Abstract 10390: Prasugrel Treatment is More Effective in Reducing Platelet Reactivity in PCI Patients with Low Clopidogrel Response Compared to Dose Increase of Clopidogrel American Heart Association (AHA) 2011 Scientific Sessions, Orlando, Florida

Study sponsored by Daiichi Sankyo

MDV3100 extends life in men with prostate cancer post chemotherapy

Positive results for MDV3100, a novel, oral androgen-receptor signalling inhibitor, were announced recently at the American Society for Oncology (ASCO) Genitourinary (GU) Cancers Symposium in San Francisco, California.

In the full interim analysis of the phase III AFFIRM study,[1] MDV3100, extended life by nearly five months (the primary endpoint of the study), was well tolerated and met all secondary endpoints. Secondary endpoints in the study included radiographic progression-free survival (rPFS) and time to prostate-specific antigen (PSA) progression. A median rPFS of 8.3 months was seen in the MDV3100 group compared to 2.9 months for placebo. There was a statistically significant ($p<0.0001$) improvement in time to prostate-specific antigen (PSA) progression (8.3 months versus 3.0 months). In addition, PSA declines of 50% or greater were more common in the MDV3100 group than in the placebo group (54.0% versus 1.5%), as were PSA declines of 90% or greater (24.8% versus 0.9%).

MDV3100 was well tolerated by patients with the majority of adverse events (type and frequency) being comparable to placebo. Common side effects included fatigue, diarrhoea and hot flushes. Adverse events of interest included fatigue (6.3% in the MDV3100 group versus 7.3% in the placebo group), cardiac disorders (0.9% versus 2.0%) including myocardial infarction (0.3% versus 0.5%), seizure (0.6% versus 0.0%) and liver function test abnormalities (0.4% versus 0.8%).

Trial sponsored by Astellas Pharma Europe Ltd and Medivation, Inc.