The Dal-GenE-2 Study: dalcetrapib and pharmacogenomic precision medicine in cardiovascular disease

Dalcetrapib, an investigational therapy that acts on CETP, is being developed by DalCor Pharmaceuticals as the first pharmacogenomic precision medicine in cardiovascular disease. It has been extensively studied in more than 20,000 patients in randomised controlled clinical trials and has been shown to be well tolerated.

Dalcetrapib is currently being evaluated in the dal-GenE-2 study, a confirmatory Phase 3 cardiovascular outcomes trial. This study is evaluating the effect of dalcetrapib to reduce fatal and non-fatal MI in 2,000 patients with a recent acute coronary syndrome and the AA genotype at variant rs1967309 in the ADCY9 gene. A companion diagnostic test, developed in conjunction with Roche Molecular Systems, identifies patients with the ADCY9 AA genotype who may potentially benefit from dalcetrapib treatment for this study.

In 2012, following the early stopping for futility of a study called dal-OUTCOMES, a retrospective genetic analysis was conducted in a subset of dal-OUTCOMES patients who provided DNA samples. A significant association was found between the effects of dalcetrapib on cardiovascular disease and a variation in the ADCY9 gene on chromosome 16, specifically, at the DNA locus rs1967309 which is within the gene there are two variants 'A' and 'G'. The group of subjects with two copies of the A variant had a reduction of 39% in combined cardiovascular outcomes on dalcetrapib compared to placebo. Conversely, no benefit was observed for the AG genotype while subjects with the GG genotype showed a 27% increase in cardiovascular events. This effect associated with the ADCY9 AA genotype was seen only in subjects on dalcetrapib and was not observed in the placebo group. This is consistent with the ADCY9 genotype not being an independent predictor of cardiovascular risk

Further retrospective work from dal-OUTCOMES indicated differences by ADCY9 genotype for CRP with dalcetrapib treatment. Data from a second study, dal-PLAQUE 2, found more cholesterol efflux and less atherosclerotic progression to be associated with dalcetrapib treatment in patients with the ADCY9 AA genotype.

The hypothesis of ADCY9 and CETP interaction with dalcetrapib was then prospectively tested in the dal-GenE study (dal-301), which investigated the effects of dalcetrapib compared to placebo in 6149 post-ACS patients with the ADCY9 AA genotype. Treatment with dalcetrapib did not demonstrate a statistically significant result, with the composite primary endpoint of CV events occurring in 9.5% of patients in the dalcetrapib group, compared with 10.6% in the placebo group.

While the dal-GenE trial missed the primary endpoint, the results showed a 21 % relative risk reduction in fatal and non-fatal MI. Pre-specified analyses also revealed a 23% relative risk reduction in the composite primary endpoint for those with type 2 diabetes and a 41 % reduction in patients in North America. Additionally, the results of the study further confirmed the reassuring safety profile of dalcetrapib.

In summary, these results have led to the implementation of the ongoing dal-GenE-2 (dal-302) Phase 3 trial which is being conducted under an agreed Special Protocol Assessment by the FDA. The study will assess dalcetrapib' s potential to reduce fatal and non-fatal MI in 2,000 North American patients with a recent acute coronary syndrome and the AA genotype at rs1967309 in the ADCY9 gene. Positive data from the dal-GenE-2 study will support a potential FDA new drug application.

References

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