Alkaline Phosphatase Levels Predict Adverse Cardiovascular Outcomes and Cognitive Impairment in High Risk Patients


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Background

Serum alkaline phosphatase (ALP) is associated with incident cardiovascular disease (CVD), coronary artery disease, vascular calcification, cerebral small vessel disease and ischemic stroke. Recent studies also associate elevated ALP with impaired cognition, suggesting neuronal or neurovascular dysfunction. To date there is no specific pharmacological means to lower ALP. Bromodomian & extramaterial (BET) proteins bind to acetylated histones on chromatin and regulate gene transcription. Apabetalone targets the second bromodomain of BET proteins and inhibits expression of genes that participate in vascular inflammation and calcification, coagulation and the complement pathway (Figure 1). In CVD patients (pts), apabetalone lowers serum ALP in a dose-dependent manner.

Methods

In Phase 2 apabetalone studies (n=795) up to 26 weeks’ duration in patients with CVD, we assessed the relationship of ALP and CVD events.

In the recently completed Phase 3 BETonMACE study with apabetalone (n=2,419), baseline cognitive function (Montreal Cognitive Assessment, MoCA) and ALP were measured in pts aged 70 yrs and older (n=469).

Results: ALP and MACE in Phase 2 Studies

In Phase 2 studies:

- Median baseline ALP was 72 U/L. Baseline ALP (dichotomized at 72 U/L) predicted the risk of MACE (Figure 2).
- Apabetalone treatment lowered CVD events (death, non-fatal MI, coronary revascularization, or hospitalization for CV cause) by 44% (p=0.02) (Figure 3).
- ALP was unaffected by treatment with placebo (PBO), but was lowered by a mean of 6.6 U/L (7.9%) from baseline after 12-24 weeks, and by 6.9 U/L (7.9%) from baseline after 24-26 weeks by apabetalone (all p-values <0.0001) (Figure 4).
- Baseline ALP predicted CVD events, independent of high-sensitivity C-reactive protein (hsCRP), sex, age, race, study, cardiovascular risk factors, chronic kidney disease (CKD), liver function markers, and treatment allocation (hazard ratio [HR] per standard deviation [SD] 1.6, 95% CI 1.2 – 2.2, p<0.002).
- A 1 SD (13.0 U/L) reduction in ALP with apabetalone was associated with a MACE HR of 0.68 (95% CI 0.49 – 0.93, p=0.02) (Figure 5).

Summary and Conclusions

Serum ALP is associated with risk of MACE in patients with CVD. Apabetalone is a BET-inhibitor that lowers serum ALP in CVD pts. In Phase 2 studies, reduction of ALP and CVD events with apabetalone were associated. The current hypothesis-generating findings raise the possibility that ALP-lowering by apabetalone contributes to CVD event reduction.

The effects of apabetalone on MACE and cognitive function (via MoCA) will be reported from the recently completed Phase 3 BETonMACE trial.