Effect of the BET Protein Inhibitor Apabetalone on Serum Markers of Potential Importance for Cognitive Decline in Cardiovascular Disease Patients

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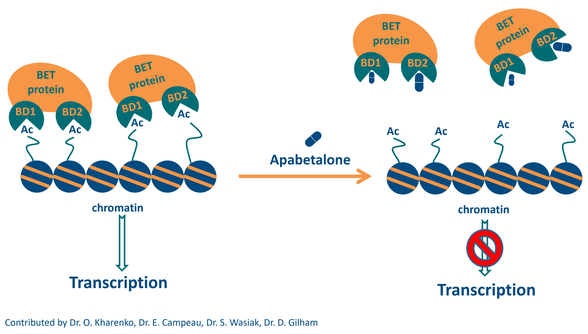
Background

Preventing and treating vascular cognitive impairment (VCI) has been challenging and thus novel therapeutic targets and approaches are currently being explored. Recent findings indicate a potential role of bromodomain and extraterminal (BET) proteins in VCI pathogenesis and Aβ metabolism. Apabetalone (RVX-208) has previously been shown to downregulate markers of vascular inflammation, vascular calcification, complement and coagulation contributing to their effects on vascular disease pathogenesis. Apabetalone inhibits the interaction between BET protein bromodomains (BD) and acetylated lysine on histones or transcription factors. Apabetalone is a selective (BD2) BET inhibitor (BETi). BET proteins control the recruitment of the transcriptional machinery to coordinate gene transcription of BET sensitive genes, including factors responsive to inflammatory insult. Less is known about direct or indirect effects of BETi on Aβ metabolism. In phase 2 trials apabetalone treatment showed a significant reduction in major adverse cardiovascular events (MACE). The MACE reduction was most pronounced in patients with diabetes and elevated inflammation. Therefore a phase 3 outcomes trial - BETonMACE - has been initiated in post-acute coronary syndrome (ACS) patients with diabetes. The primary endpoint is time to cardiovascular disease (CVD)-related death, non-fatal myocardial infarct or stroke. Cognition assessment by Montreal Cognitive Assessment (MoCA) is being evaluated in patients ≥70 years of age in BETonMACE. Effects of apabetalone on MoCA will provide insights about the potential for BETi to modulate cognitive function in elderly patients with cardiovascular disease and diabetes.

Apabetalone Mechanism of Action



Contributed by Dr. O. Kharenko, Dr. E. Campeau, Dr. S. Wasiak, Dr. D. Gilham

BET proteins bind acetylated lysine (Ac) on histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes which drives inflammation and other key markers of cognitive decline. Apabetalone inhibits BET proteins, causing release from chromatin and downregulation of BET sensitive gene expression.

Pill size: selectivity of apabetalone for BD2

Methods

Serum Aβ40 was assessed in apabetalone phase 1 and 2 clinical trials. Serum Aβ40 was analyzed in phase 2 clinical dose-response trial ASSERT before and after 12 weeks treatment in a stable coronary artery disease population of 299 patients using Invitrogen ELISA assay. In addition, SOMAscan™ proteomic analysis was performed on serum from the Phase 2b ASSURE clinical trial to assess levels of ~1,300 proteins in the plasma following 26 weeks of treatment. Proteins of interest were selected based on literature describing their link to pathogenesis of VCI, MCI and/or AD.

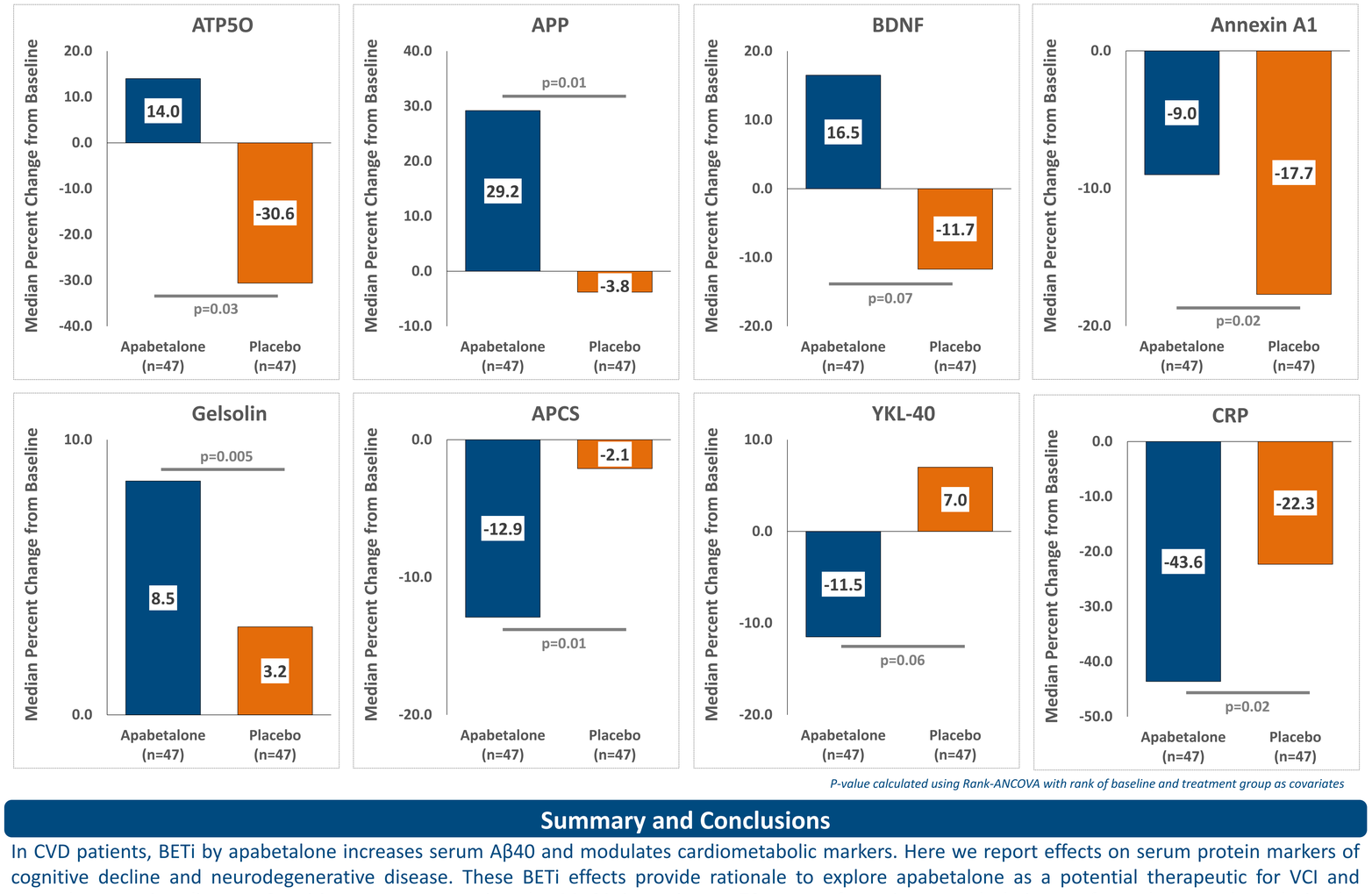
Objective

We investigated the effect of apabetalone on serum markers of cognitive decline and neurodegenerative disease progression from archived serum samples from a phase 2 trial in patients with CVD. These findings provide rationale for a cognition sub-study of the ongoing BETonMACE clinical trial.

Results

In a Phase 1 clinical trial (test study) 8 mg/kg treatment per day for 7 days resulted in an 11.4% (SD 3.0) increase in serum Aβ40 vs. 2.2% (SD 5.8) for placebo. In the ASSERT Phase 2 trial (confirmation study), in patients with the lowest serum Aβ40 level at baseline (below median), treated with a dose of 150 mg, b.i.d., a significant increase of +7.7% in serum Aβ40 was observed in the apabetalone-treatment group (n=30) compared to placebo (n=30). At doses of 50 mg b.i.d. and 100 mg b.i.d, serum Aβ40 increases of +0.8% and +4.5% were observed, respectively. The Invitrogen ELISA method for Aβ42 used was not sufficiently sensitive for detecting serum levels.

We have previously reported changes in the plasma proteome of patients treated with apabetalone in the complement and coagulation pathways, the acute phase response and vascular inflammation. Here we report, for the first time, changes in proteins linked to cognitive decline and neurodegenerative disease. In the atherosclerosis regression phase 2 ASSURE trial, proteomic analysis demonstrated significant increases in the apabetalone (n=47) group (100 mg b.i.d.), versus placebo treated (n=47) patients in the following markers; ATP synthase subunit O-mitochondrial (ATP5O) +45%; Amyloid Beta A4 Protein (APP) +33%; Brain-Derived Neurotrophic Factor (BDNF) +28%; Annexin A1 +9%; and Gelsolin, +5% ($p<0.05$ for all markers, except BDNF, which had $p<0.1$). The following markers were decreased versus placebo: Serum Amyloid P-Component (APCS) -11%; tyrosine (Y), lysine (K) and leucine (L) 40kDa (YKL-40) (CHI3L1), -18.5%; and C-Reactive Protein (CRP), -21% ($p<0.05$ for APCS and CRP; YKL-40 $p<0.1$).



P-value calculated using Rank-ANCOVA with rank of baseline and treatment group as covariates

Summary and Conclusions

In CVD patients, BETi by apabetalone increases serum Aβ40 and modulates cardiometabolic markers. Here we report effects on serum protein markers of cognitive decline and neurodegenerative disease. These BETi effects provide rationale to explore apabetalone as a potential therapeutic for VCI and neurodegenerative disease. Cognition assessment using the MoCA in patients ≥70 years of age is currently being performed as a sub-study in the BETonMACE Phase 3 CVD outcomes trial. Favorable effects on cognition coupled with mechanistic understanding would open developmental paths for confirmatory trials in VCI and neurodegenerative disorders.