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Lowering the neutrophil to lymphocyte ratio by the BET inhibitor, apabetalone: potential implications for cardiovascular events in high risk patients

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Background: In addition to traditional inflammatory markers, the neutrophil to lymphocyte ratio (NLR) has been identified as a marker of systemic inflammation. Higher NLR has been associated with adverse clinical outcomes and is predictive of incident events in patients with CVD, diabetes and CKD. Apabetalone selectively inhibits the second ligand domain in bromodomain and extra terminal (BET) proteins, which are epigenetic readers of acetylated lysine marks on histone tails. Apabetalone modifies inflammatory pathways implicated in vascular disease and reduces incidence of major adverse cardiovascular events (MACE: death, non-fatal myocardial infarction and hospitalization for cardiovascular causes) in pooled data from phase 2 studies (SUSTAIN & ASSURE, n=499).
Purpose: To evaluate the impact of apabetalone treatment on the NLR and its association with MACE.
Methods: Neutrophil and lymphocyte counts were collected in the haematology panels during two phase 2 trials: SUSTAIN and ASSURE, which compared the effects of treatment with apabetalone 200 mg bid (n=331) and placebo (n=168) for up to 26 weeks on circulating cardiovascular biomarkers and atherosclerotic plaque in patients with established CVD (n=499).
Results: During the course of the trials, patients that experienced a MACE (n=36) were identified to have a higher baseline NLR compared with those patients who did not experience a MACE (n=463; 2.8 vs. 2.4, p<0.05). After 3 months of treatment, reductions in the NLR were observed with apabetalone treatment compared to placebo (-8.0%, p<0.001 vs baseline in apabetalone group and -1.0%, ns vs baseline in placebo group). The NLR improvement was sustained at 6 months (-7.5%, p<0.001 vs baseline in apabetalone group and -3.5%, ns vs baseline in placebo group). Consistently, in the diabetes patients in the phase 2 studies (n=127 in apabetalone group; n=65 in placebo group), similar reductions in the NLR were observed with apabetalone treatment compared to placebo (-7.0%, p<0.10 vs baseline in apabetalone group and +6.3%, ns vs baseline after 6 months of treatment).
Conclusions: Baseline NLR levels were higher in patients with established CVD that experienced a MACE during the 6 months SUSTAIN and ASSURE apabetalone intervention studies. Apabetalone treatment in these studies reduced NLR in the all and in the diabetes subpopulation highlighting its impact on inflammatory pathways implicated in CVD, and supports previously published anti-inflammatory effects observed with apabetalone treatment. The effect of apabetalone on reducing MACE outcomes is being evaluated in the ongoing phase 3 BETonMACE study.