<S10-2>

Comparing the Results and Implications of Recent PCSK9 mAb Cardiovascular Outcomes Trials

Nathan D. Wong
University of California, USA

Monoclonal antibody (mAb) therapy for proprotein covertase subtilisin-like kexin type 9 (PCSK9) have been shown to reduce LDL-C by 55-60% on average over moderate and high intensity statin therapy in in persons with atherosclerotic cardiovascular disease (ASCVD), with reductions of 40-50% observed in those with heterozygous familial hypercholesterolemia. In the past two years, several major trials of PCSK9 mAb therapy on ASCVD outcomes have been reported out. The GLAGOV trial completed 846 patients with established ASCVD who were randomized to statin monotherapy or statin plus evolocumab 420 mg once monthly and completed baseline and 18-month repeat intravascular ultrasound. This trial met the primary endpoint of percent atheroma volume reduction, which changed by -0.95 in the intervention compared t o 0.05 in the control arm ($p<0.0001$); the secondary endpoint of total atheroma volume was also significantly reduced and among intervention group participants 64.3% showed regression of their plaque compared to 47.3% of control group participants. This trial was followed by the release of the FOURIER trial of 27,564 patients with established stable ASCVD with an LDL-C>70 mg/dl (or non-HDL-C of >100 mg/dl) on moderate or high intensity statin therapy. FOURIER met its primary composite ASCVD endpoint with a 15% relative risk reduction (and absolute risk reduction of 1.5%) after a median of 2.2 years of follow-up. Landmark analyses showed a further divergence and greater relative risk reductions after the first year of therapy. Subsequent subgroup analyses have shown similar benefits on reducing ASCVD outcomes in those with vs. without diabetes, and greater benefits in those with a more recent baseline ASCVD event (within 2 years), multiple ASCVD events, peripheral arterial disease, as well as those with multiple vessel disease. There was also increased efficacy and demonstrated safety in the subgroup achieving LDL-C levels of <10 mg/dl. Moreover, the EBBINGHAUS substudy of cognitive function showed no difference in change/ decline of cognitive function between evolocumab and control group subjects. Cardiovascular outcomes from the PCSK9 mAb, bococizumab were reported from the early termination of the SPIRE-1 (patients with LDL-C >70 mg/dl) and SPIRE-2 (patients with LDL-C >100 mg/dl) trials. Whereas SPIRE-1 showed no benefit, there was a 21% statistically significant relative risk reduction seen in SPIRE-2; however, due to attenuated response over time in LDL-C, both trials were terminated early and bococizumab was discontinued from further clinical development. Finally, the ODYSSEY Outcomes Trial randomized 18,924 patients with an acute coronary syndrome within the past year to alirocumab versus placebo if LDL-C remained at least 70 mg/dl (or non-HDL >100 or apolipoprotein B >80 mg/dl) after high intensity statin therapy. The primary ASCVD endpoint was reached after a median of 2.8 years, with a 15% relative risk reduction. Of note, there was a greater 24% relative risk reduction in the pre-specified group with a baseline LDL-C >100 mg/dl. In addition, all-cause mortality was lower by 15%. The results of the above studies showed PCSK9 mAb therapy (except for bococizumab) is efficacious in not only retarding progression or eliciting regression of atherosclerosis, but also reducing subsequent ASCVD events, especially in higher risk individuals.