PCSK9 mAbs or even vaccines – the new statins?

LONDON, UK----18th March 2013----ExpertREACT. Novel PCSK9 (proprotein convertases subtilisin/kexin type 9) inhibitors, such as Sanofi's anti-PCSK9 monoclonal antibody SAR236553, have impressive LDL-C reducing efficacy. PCSK9 vaccines may represent an alternative strategy to the monoclonal antibody approach, taking a share of the multibillion-dollar PCSK9 market.

Cardiovascular disease (CVD), is the leading cause of death in high income countries[1,] and by 2030, around 40% of the US population are projected to have some form of CVD with direct medical costs of $818 billion[2]. Raised low-density lipoprotein cholesterol (LDL-C), smoking, and uncontrolled hypertension are major risk factors the development of CVD, and some 50% of US adults have at least one of these risk factors[3.]

Statins are the most effective drug class for reducing LDL-C, with the choice and dose of statin reflecting the degree of LDL-C reduction that is required to reach target LDL-C goals. LDL-C treatment goals are directly related to the level of CVD risk, with high-risk patients having the most demanding LDL-C targets. High-risk patients include those with acute coronary syndrome, non-coronary atherosclerosis (such as peripheral arterial disease and ischemic stroke), and heterozygous familial hypercholesterolemia (heFH), one of the most common hereditary metabolic disorders with a frequency in persons of European descent of ~1 in 500.

The joint European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) dyslipidemia guidelines[4] recommend a target LDL-C goal of <1.8mmol/L (<70mg/dL) in high-risk patients with CVD (a lower limit at which LDL-C reduction fails to decrease CV risk has not been determined[5]). Based on current clinical practice, however, only ~30-40% of CVD patients achieve this LDL-C goal[6]. It is likely that more patients could reach the target LDL-C goal if they were prescribed the most potent statins at the highest tolerable dose, or a second LDL-C lowering drug, such as Merck's Zetia (ezetimibe), was added. Even with optimal use of available LDL-C lowering drugs, **VacZine Analytics** estimate that at least 50% of high-risk patients are unable to achieve the recommended LDL-C goal. The LDL-C goal set by clinical practice guidelines is beyond the limit of efficacy of currently approved therapies and novel therapeutic strategies will be required to achieve target LDL-C levels in all high-risk patients.

Several novel LDL-C lowering treatments are in clinical development: Pfizer, Sanofi, Amgen, Roche and Alnylam are all developing PCSK9 (proprotein convertases subtilisin/kexin type 9) inhibitors. Sanofi's SAR236553, a twice-monthly subcutaneously administered anti-PCSK9 monoclonal antibody, is the most clinically advanced PCSK9 inhibitor (Sanofi licensed SAR236553 from Regeneron Pharmaceuticals). In a phase 2 trial, SAR236553 added to statin therapy further reduced LDL-C by 40-72%[7]. This represents a significant advance in LDL-C lowering efficacy, considering Zetia lowers LDL-C by an additional 15 to 20% when added to statin therapy.

A global launch of SAR236553 is expected in 2016. The FDA/EMEA are expected to approve SAR236553 without data from the ongoing CV outcomes trial (which should report in 2018): other non-statin LDL-C lowering drugs, such as Zetia, received regulatory approval based on a reduction in LDL-C as a surrogate outcome of CV risk reduction.

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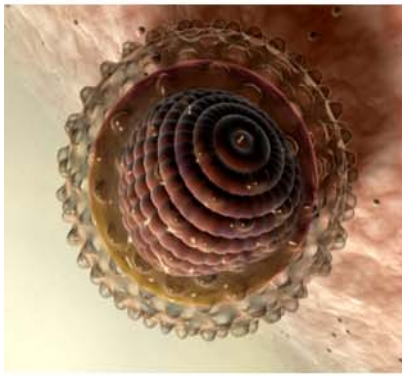

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A key question is whether any safety signals arise with SAR236553, which could impact the regulatory risk/benefit analysis. If approved, SAR236553 would probably be used as an adjunct therapy in high-risk patients who fail to achieve the target LDL-C goal on a statin plus a second LDL-C lowering treatment, or those who are statin intolerant.

PCSK9 vaccines could potentially induce functional PCSK9 antibodies to lower LDL-C. No PCSK9 vaccines are in active clinical development, although Pfizer has claimed patents for a PCSK9 vaccine and AFFiRiS AG (Austria) is developing a peptide-based PCSK9 vaccine. Several questions remain about the PCSK9 vaccine approach, such as the dosing required to achieve therapeutically-relevant levels of PCSK9-specific antibodies, the possible variability of antibody response between patients and the frequency of boosting required to prevent levels of circulating PCSK9 antibody falling below the desired level. Assuming PCSK9 vaccination is feasible in humans, **VacZine Analytics** research[8] suggest vaccine players could attain a lucrative share of the forecast multibillion-dollar market for novel PCSK9 therapies.

*__Top 5 companies:__ GSK Biologicals, Sanofi Pasteur, Merck & Co, Pfizer (Wyeth) and Novartis Vaccines and Diagnostics

References and Notes:

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