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PCSK9 antibodies: A new therapeutic option for the treatment of hypercholesterolemia

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The serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) was initially identified in 2003. At the same year, Abifadel et al. described two mutations in the PCSK9 gene causing autosomal dominant hypercholesterolemia in two French families. In 2006, Cohen et al showed that PCSK9 mutations are associated with low LDL-cholesterol (LDL-C) concentrations and reduced cardiovascular risk. In specific, 2.6% of the black subjects examined (N=3363) had nonsense mutation in *PCSK9*. These mutations were associated with the mean plasma LDL-C being 28% lower, compared to non-carriers, and associated with an 88% reduction in the risk of coronary heart disease (CHD). Similarly, 3.2% of the white subjects examined (N=9524) had a sequence variation in *PCSK9* that was associated with a 15% reduction in LDL-C and a 47% reduction in the risk of CHD.

PCSK9 regulates the levels of circulating LDL-C by increasing the degradation of the hepatic LDLR by lysosomess. Therefore, it could be reasonable to expect that PCSK9 inhibition would be associated with a reduction of LDL-C levels. Cardiovascular endpoint trails with two fully human monoclonal antibodies targeting PCSK9, namely evolocumab developed by AMGEN and alirocumab developed by Sanofi/Regeneron, are expected to have results in 2017 and 2018, respectively. A large number of phase II and III studies testing show a significant reduction in LDL-C levels of ~50-70%. In 2015 both drugs, evolocumab (Repatha®), and alirocumab (Praluent®), have been approved by the Food and Drug Administration (FDA) and by the European Medicine's Agency (EMA) for use in a rather wide range of patients. In particular, in the US they are approved as adjunct to diet and maximaly tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (heFH) or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL-C. In Europe they are approved for the treatment of adults with primary hypercholesterolemia (familial or non-familial) or mixed dyslipidemia on top of dietary therapy in combination with a statin or with a statin and other lipid-lowering therapies (LLT), for patients that cannot achieve their LDL-C targets and as monotherapy or combined with other LLT in patients with statin intolerance or in those with a contraindication for the use

of a statin. Both in Europe and in the US evolocumab is also approved for the treatment of homozygous FH (hoFH) in adults and children older than 12 years of age in combination with other LLT.

In this talk I will present some selected important phase 3 trials of alirocumab (formerly REGN727/SAR236553) and evolocumab (formerly AMG 145).

Phase III trials with evolocumab

PCSK9 inhibition with evolocumab in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial

Purpose of this randomised, double-blind, placebo-controlled trial was to examine the effects of evolocumab on LDL-C levels in patients with heFH. Patients (n=331, mean age 51 years, 42% female, 31% with CHD) with heFH diagnosed clinically using the Simon Broome criteria, on stable LLT and a fasting LDL-C concentration of ≥100 mg/dL (mean baseline LDL-C 154 mg/dL) were randomized to receive SC evolocumab 140 mg Q2W (n=111), evolocumab 420 mg QM (n=110), or SC placebo every 2 weeks (n=55) or once a month (n=55) for 12 weeks. We found that evolocumab at both dosing schedules led to a significant reduction in mean LDL-C compared to placebo. In specific, the Q2W dose was associated with a 59.2% reduction, and the QM dose with a 61.3% reduction ($p<0.0001$ for both) at week 12. More than 60% of the patients achieved an LDL-C of < 70 mg/dL. Statistically significant Lp(a) and triglyceride decreases as well as increases in HDL-C were seen in both Q2W and QM dosing groups. In specific, Lp(a) decreased by up to 31.6% from baseline vs placebo, triglycerides by up to 22.4% and HDL-C increased by up to 9.5% (all $p<0.0001$). Evolocumab was well tolerated, with rates of AEs similar to placebo. The most common AEs occurring more frequently in patients receiving evolocumab were nasopharyngitis (9% vs 5% in the placebo group) and muscle-related AEs (5% vs 1%, respectively). We also performed a genetic analysis of the mutation-causing FH which showed that the response to evolocumab was independent of the underlying genetic mutation.

Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial

HoFH is a rare disease (incidence 1: 300.000 to 1:1.000.000) caused by very low or absent removal of LDL from the plasma due, in the majority of the cases, to defective LDLR function, and is associated with very high circulating LDL-C concentrations, and development of CVD early in life [32]. Currently available LLT are modestly effective, at best, in this patient population. Evolocumab has been shown in a small study to reduce LDL-C in patients with hoFH by 16% [33]. Aim of this randomised, double-blind, placebo-controlled trial was to examine the effects of evolocumab in patients with hoFH (n=49, mean age 31 years, 49% female, 90% white, 43% with CHD), on stable LLT for ≥ 4 weeks (63% were on ≥ 40 mg atorvastatin, 31% on ≥20 mg rosuvastatin and 92% on ezetimibe) but not on apheresis. The patients were randomized to receive evolocumab 420 mg or placebo QM for 12 weeks. LDL-C was measured by ultracentrifugation. Mean baseline LDL-C was 348 mg/dL. Evolocumab reduced LDL-C at 12 weeks by 30.9% ($p<0.0001$), an absolute decrease of 93 mg/dL. HDL-C and triglyceride levels did not change. The trial also examined the LDL-C reduction based on the underlying genetic mutation. Patients with mutations associated with less than 2% of normal LDL uptake were classified as receptor negative and those with 2–25% of normal uptake as receptor defective [34]. The one patient who had a mutation associated with no receptor activity (receptor negative), did not respond to evolocumab at all. The majority of patients however, had at least one LDLR-defective mutation and showed an LDL-C reduction of 40.8% ($p<0.0001$) with those having two LDLR-defective genes achieving a reduction of 46.9% ($p=0.0006$), a rather impressive decrease for this difficult to treat population. TEAEs occurred in 63% of patients in the placebo group and in 36% in the evolocumab group. There were no SAEs during the study.

Efficacy and safety of evolocumab in reducing lipids and cardiovascular events

In this paper the results of the Open-label Study of Long-term Evaluation against LDL-C 1 (OSLER-1) (for patients that had participated in at least one of five phase2 trials with evolocumab), and of OSLER-

2 (for those that had participated in at least one of seven phase 3 trials) are reported. These were two extension studies that were performed to obtain longer-term safety and efficacy data and also included a prespecified exploratory analysis on adjudicated cardiovascular outcomes (including death, MI, unstable angina, coronary revascularization, stroke, transient ischemic, attack, and heart failure). In these two open-label, randomized trials 4465 patients (mean age 58 years, 50% female, 86% white, 20% with CHD, median baseline LDL-C 120 mg/dL) were enrolled. Eligible patients were randomly assigned to receive either evolocumab (140 mg Q2W or 420 mg QM) plus standard therapy or standard therapy alone. Median follow-up was 11.1 months. Data from the two trials were combined. The results showed that evolocumab, compared with standard therapy alone, caused a 61% reduction in LDL-C concentrations (P<0.001). The majority of AEs occurred with similar frequency in the two groups. However, neurocognitive events (including delirium, confusion, cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders) were reported more frequently in the evolocumab than the standard therapy group (0.9% vs 0.3%, respectively). There was no association between achieved LDL-C levels and adverse events. After 11 months a prespecified exploratory analysis showed that there was a 53% decrease in the cumulative incidence of CVD events (p=0.003) in the patients receiving evolocumab compared with those receiving standard therapy. Of note the number of events these calculations are based on is rather small (cardiovascular events were reported in 29 of 2976 patients in the evolocumab group and in 31 of 1489 patients in the standard-therapy group)

Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance. The GAUSS-3 randomized clinical trial

It is known that 5% to 10% of statin-treated patients report intolerance, mostly due to muscle-related AEs. Purpose of the GAUSS-3 trial, a phase 3, multicenter, two-stage, randomized, double-blind, ezetimibe-controlled study was to identify patients with muscle symptoms confirmed by statin rechallenge and to compare effectiveness of 24 weeks of evolocumab 420 mg QM vs ezetimibe 10 mg daily in hypercholesterolemic patients unable to tolerate an effective statin dose. We have recently published the design of the trial.

Briefly, this study incorporates a novel atorvastatin-controlled, double-blind, crossover phase to objectively identify statin intolerance. Eligible patients had LDL-C above the National Cholesterol Education Project (NCEP) Adult Treatment Panel III (ATP III) target level for the appropriate CHD risk category and were unable to tolerate ≥3 statins or 2 statins (one of which was atorvastatin ≤10 mg/d) or had a history of marked CK elevation accompanied by muscle symptoms while on 1 statin. We recruited 511 patients with uncontrolled LDL-C levels and history of intolerance to ≥ 2 statins. Phase A used a 24-week crossover procedure with atorvastatin 20 mg or placebo to identify patients having symptoms only with atorvastatin but not with placebo. Phase A was followed by a 2-week washout and then phase B started (only patients that had muscle symptoms on atorvastatin but not on placebo could progress to phase B). In this part of the trial patients were randomized to ezetimibe (10 mg/daily) or evolocumab (420mg QM) for 24 weeks. Four hundred and ninety one patients entered phase A (mean age 61 years, 50% women, 95% white, 35% with CHD). From them 209 (42.6%) reported muscle symptoms while taking atorvastatin but not while taking placebo. Of these, 199 entered phase B (mean age 59 years, 51% women, 95% white, 32% with CHD). Nineteen subjects proceeded directly to phase B due to a documented history elevated CK more than 10XULN. A total of 73 subjects were randomized to ezetimibe and 145 to evolocumab. The mean entry LDL-C level was 219.9 mg/dL. The mean % change from baseline in LDL-C at weeks 22 and 24 was 16.7% with ezetimibe and 54.5% with evolocumab (p<0.001) (absolute decrease in LDL-C of 31.0 mg/dL and 106.8 mg/dL for ezetimibe and evolocumab, respectively, p<0.001). The mean % change from baseline in Lp(a) was -1.6% with ezetimibe and -22.7% with evolocumab (p<0.001) and in HDL-C +1.7% with ezetimibe and +7.8% with evolocumab (p=0.008). There were no between-group differences in triglycerides. Active study drug was discontinued for muscle symptoms in 6.8% of patients on ezetimibe and in 0.7% of those on evolocumab. This study clearly showed that in patients with statin intolerance due to muscle-related adverse effects, evolocumab decreases LDL-C levels significantly more (between-group

difference of ~40%) than ezetimibe (p<0.001). Interestingly 25.5% of the patients developed intolerable muscle symptoms while taking placebo but not atorvastatin, 9.8% developed symptoms with both placebo and atorvastatin and 17.3% had no symptoms with either treatment.

Phase III trials with alirocumab

Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial

Purpose of this randomized, double-blind, double-dummy, parallel-group trial in patients with hypercholesterolemia at high or very-high CVD risk on a stable dose of atorvastatin 20 mg or 40 mg was to compare the effects of adding alirocumab compared to using other commonly prescibed LLT on LDL-C levels. Patients (n=355, mean age 63 years, 35% female, 86% white) with CVD and LDL-C levels ≥70 mg/dL, or CVD risk factors and LDL-C ≥100 mg/dL, were randomized to receive (on top of atorvastatin 20 or 40 mg), either alirocumab 75 mg Q2W SC or ezetimibe 10 mg/day or to doubling the atorvastatin dose or, for the atorvastatin 40 mg regimen only, to switching to rosuvastatin 40 mg. If patients at week 8 had not achieved their LDL-C treatment goal (≤70 mg/dL for patients with CVD and ≤100 mg/dL for patients without), the dose of alirocumab was increased in a blinded manner at week 12 to 150 mg Q2W. We found that addition of alirocumab reduced LDL-C levels at week 24 by 44.1% and 54.0% in patients on 20 mg and 40 mg atorvastatin, respectively (p<0.001). Addition of ezetimibe reduced LDL-C levels by 20.5% and 22.6%, respectively, in the two atorvastatin groups, while doubling of the atorvastatin dose (20 to 40 mg and 40 to 80 mg) achieved a further 5.0% and 4.8% LDL-C reduction, respectively. Switching atorvastatin 40 mg to rosuvastatin 40 mg was associated with a 21.4% further decrease in LDL-C levels. LDL-C goals were achieved by 87.2% and 84.6% of the patients on alirocumab (in the 20 mg and 40 mg atorvastatin group, respectively). There were no significant changes with alirocumab treatment in HDL-C and in triglyceride levels. There was a significant (p<0.001) decrease in Lp(a), ranging from 21.1 to 31.0% when compared with all comparators on a background of atorvastatin 40 mg. Only 14% of the patients on alirocumab required an increase of the dose to 150 mg. TEAEs were observed in 65.4% of patients receiving alirocumab, in 64.4% of patients receiving ezetimibe and in 63.8% of the patients that doubled their atorvastatin dose or were switched to rosuvastatin.

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events (ODYSSEY LONG TERM)

Purpose of this large (n=2341, mean age 61 years, 38% female, 93% white, 69% with CHD), randomized, double-blind, placebo-controlled, parallel-group study was to examine the safety and efficacy of alirocumab over a longer period of time (78 weeks). The patients included in the study were at high risk for cardiovascular events, had LDL-C levels of ≥70 mg/dL and were already on maximally tolerated statin therapy with or without other LLT (14.4% were also on ezetimibe). Mean LDL-C at baseline was 122 mg/dL. HeFH was present in 17.7% of the patients, 34.4% diabetes mellitus type 2 and 41.0% had CHD equivalents. The latter were defined as PAD, ischemic stroke, moderate chronic kidney disease [estimated glomerular filtration rate (eGFR), 30 to <60 ml/min/per 1.73m^2 of body-surface area], or diabetes mellitus plus two or more additional risk factors [hypertension, ankle-brachial index (ABI) of ≤0.90, microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein, retinopathy (preproliferative or proliferative retinopathy or having had laser treatment for retinopathy) or a family history of premature CHD]. The patients were randomly assigned in a 2:1 ratio to receive alirocumab 150 mg or placebo Q2W for 78 weeks. Seventy two percent of the patients completed the study. At week 24 (primary endpoint) there was a 61% reduction in the alirocumab group and a 0.8% increase in the placebo group (p<0.001). The percent decrease in LDL-C level in the alirocumab group at week 78 was 52.4%. Alirocumab significantly reduced Lp(a) by 25.6% (p<0.001), triglycerides by 17.3% (p<0.001) and increased HDL-C by 4.6% (p<0.001). Patients receiving alirocumab compared to those receiving placebo had higher rates of ISRs (5.9% vs. 4.2%), myalgia (5.4% vs. 2.9%), neurocognitive events (defined as delirium, confusion, cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders) (1.2% vs. 0.5%), and ophthal-

mologic events (defined as optic nerve disorders, retinal disorders and corneal disorders) (2.9% vs. 1.9%), respectively. In a non-prespecified post-hoc analysis there was a reduction of 48% in adjudicated major adverse cardiovascular events [a composite of death from CHD, nonfatal myocardial infarction (MI), fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization] after 78 weeks (1.7% with alirocumab versus 3.3% with placebo; p=0.02). The cumulative incidence curves diverged progressively over time. Of note, the number of events these calcualtions are based on is quite small (27 of 1550 patients on alirocumab and 26 of 788 patients on placebo experienced an event).

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

This was a randomized, double-blind, placebo-controlled trial (N= 27,564) patients with atherosclerotic CVD and LDL-C levels of70 mg/dL or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as SC injections. The primary efficacy end point was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, MI, or stroke. The median duration of follow-up was 2.2 years. At 48 weeks, the mean percentage reduction in LDL-C levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL to 30 mg/dL (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (9.8% vs. 11.3%; HR 0.85; P<0.001) and the key secondary end point (5.9% vs. 7.4%; HR, 0.80;P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL-C levels (median, 74 mg/dL). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

Safety

The safety data from the existing trials with evolocumab and alirocumab are quite encouraging. The liver and muscle adverse events observed with statins and other lipid-lowering medications have not been seen with PCSK9 monoclonal antibodies. ISRs have been minimal and no different from placebo injections. The therapeutic use of monoclonal antibodies is always associated with the concern of developing antidrug antibodies. However, since both evolocumab and alirocumab are fully human monoclonal antibodies, this risk is expected to be rather small. However, safety questions in general will be best answered with the large, long-term phase III clinical trials of both antibodies. Questions regarding the safety of very low LDL-C levels (< 25 mg/dL) achieved by the use of anti-PCSK9 antibodies remain. Of note, Goldstein and Brown already in 1986 stated, quoting their own data, that " a level of LDL-C in plasma of 25 mg/dL would be sufficient to nourish body cells with cholesterol". In the 11 month OSLER trial Sabatine et al reported that the rate of neurocognitive adverse events was low (<1%) but still more frequent in the evolocumab group (0.9%) vs the SOC (0.3%). Robinson et al also reported in the ODYSSEY LONG-TERM trial that neurocognitive events were reported more often in the alirocumab (1.2%) vs the placebo group (0.5%). It has to be noted that the incidence of neurocognitive adverse events in both trials did not appear to be related to the LDL-C levels during treatment. Moreover, since vitamin E transport and steroidogenesis are closely associated with LDL-C metabolism, and anti-PCSK9 antibodies can lower LDL-C to very low levels, Blom et al examined the effects of evolocumab on vitamin E and steroid hormones in the 52-week, phase 3, double-blind, randomized, placebo-controlled DESCARTES study (n=901), previously described [28]. Vitamin E, cortisol, adrenocorticotropic hormone (ACTH), and gonadal hormones were analyzed in patients at baseline and at week 52. Furthermore, vitamin E levels were also measured in red blood cell membranes, in serum, in LDL, HDL, at baseline and week 52 in a substudy of 100 subjects (mean age 57 years, 52% female, 88% white, 18% with CHD). Absolute vitamin E decreased in patients treated with evolocumab by 16% but, when normalized for cholesterol, increased by 19%. In the substudy, vitamin E level changes reflected the changes in the lipid fractions. There was no change in the levels of vitamin E in the red blood cell membrane, suggesting that evolocumab treatment does not change

tissue levels of vitamin E. Cortisol increased slightly in patients treated with evolocumab, but ACTH as well as the cortisol: ACTH ratio remain unchanged. There was no change in gonadal hormones. The only statistically significant changes in female gonadal hormones were increases in LH and FSH from baseline to week 52 (P<0.005). However, there was no association between increasing LH and FSH with decreasing estradiol levels. There was no evidence of disruption in the adrenal or gonadal hormone synthesis even in patients with LDL-C levels of < 15 mg/dL. Of note, the study duration was only one year and therefore its' findings may not apply to patients treated with anti-PCSK9 antibodies for longer periods of time.

Conclusions

A large number of patients, especially those at high cardiovascular risk, those with statin intolerance (real or perceived), and those with FH, even when treated with maximally tolerated LLT can still not achieve their optimal LDL-C levels . Therefore, there is an unmet clinical need to develop novel therapeutic options to robustly reduce LDL-C levels. The anti-PCSK9 monoclonal antibodies are the most promising lipid-lowering agents since the initiation of statins. The results of the cardiovascular endpoint trials still under way the ODYSSEY Outcomes with alirocumab in patients with acute coronary syndrome (n=18,000), ecpected to be completed in 2018 will answer the question whether the robust LDL-C associated with the use of PCSK9 antibodies is translated in a decrease also of cardiovascular events and mortality. Of note, anti-PCSK9 antibodies are very expensive with yearly costs of ~$14.000 in the US and similar prices in Europe, making their wide use almost prohibitive.

With the introduction of PCSK9 antibodies we are entering an era of lipid-lowering therapies where LDL-C values can be decreased to very low levels (<25 mg/dL) and we thus have to also address the question of the long-term safety of such low LDL-C concentrations. Even though there are few individuals with no circulating PCSK9 and lifelong LDL-C concentrations of ~15 mg/dL that are apparently completely healthy, we have to await the results of the large, long-term phase III trials to be able to answer the questions about the continuing efficacy and safety of these drugs and their role in clinical practice.