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FOURIER to ODYSSEY: the end of the journey for lipid-lowering therapy trials? Lessons from recent clinical trials with anti-PCSK9 antibodies

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Despite significant progress during recent decades, cardiovascular residual risk control remains an unmet need in secondary prevention[1]. Part of the risk is related to elevated LDL-cholesterol (LDL-C) levels despite appropriate therapy (i.e., statin alone or in combination with ezetimibe). Studies with high-intensity statins and, more recently, with the combination of statins and ezetimibe have shown the correlation between intensive LDL-C lowering and residual risk reduction[2,3]. However, adverse drug reactions and the lack of sufficient decrease in hard outcomes have led to the development of a new class of lipid-lowering therapy, PCSK9 inhibitors. These new agents induce a further 50 to 70% decrease of plasma LDL-C[4] in the "not-at-target", statin-treated patients often seen by interventional cardiologists.

Evolocumab and alirocumab are two fully human anti-PCSK9 antibodies, inducing a significant and prolonged decrease of LDL-C and other atherogenic particles such as LPa, with an excellent tolerance and safety profile in phase II studies. To assess the clinical efficacy of these new agents, two phase III randomised clinical trials in secondary prevention patients were recently conducted. The results of the FOURIER study with evolocumab were released in 2017 and those of the ODYSSEY Outcomes study with alirocumab were released during the last ACC congress in 2018. The main lessons learned from these two RCTs are crucial for a better understanding of the clinical benefits and use of these new agents.

The FOURIER trial

The FOURIER trial enrolled a large spectrum of high-risk stable secondary prevention patients, not only CAD patients but also patients with PAD or in secondary stroke prevention[5]. In this study, 27,564 atherosclerotic patients with LDL-C levels of 70 mg/dL (or higher) under optimal statin therapy were randomly assigned to receive double-blinded subcutaneous injections of evolocumab (either 140 mg every two weeks or 420 mg monthly) or placebo. Evolocumab significantly reduced the risk of the primary composite endpoint (1,344 patients [9.8%] vs. 1,563 patients [11.3%]; hazard ratio [HR] 0.85, 95% confidence interval [CI]: 0.79-0.92; p<0.001) and the key secondary endpoint (MI, stroke, CV death) (816 [5.9%] vs. 1,013 [7.4%]; HR 0.80, 95% CI: 0.73-0.88; p<0.001) for a median follow-up of 26 months. The ischaemic benefits were increased over time with a higher benefit observed in the second year of treatment. Consistent with the data from the CTT meta-analysis on lipid-lowering drugs, no significant risk

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reduction was observed in relation to CV mortality or total mortality. This could be partly explained by the relatively short short-term follow-up in this trial.

ODYSSEY Outcomes trial

In the ODYSSEY Outcomes trial, 18,924 post-ACS patients (mean age 58 years), insufficiently controlled with high-dose statins (defined by LDL-C ≥70 mg/dl, or non HDL-C ≥100 mg/dl or ApoB ≥80 mg/dl), were randomised one to 12 months after the index event (median time between index ACS and randomisation 2.6 months) to receive either twice monthly injections of alirocumab (75 or 150 mg) or placebo (Steg PG; for the ODYSSEY Outcomes Investigators. Cardiovascular Outcomes with Alirocumab After Acute Coronary Syndrome: Results of the ODYSSEY Outcomes Trial. Presented at: First Late-Breaking Clinical Trial session, ACC.18, Orlando, FL, USA, 10 March 2018). Patients randomised to receive alirocumab had a double-blinded dose adjustment in order to reach the target LDL-C levels of 25-50 mg/dL. If LDL-C levels dropped consistently below 15 mg/dL, patients were switched to placebo (7.7% in the alirocumab group).

The mean follow-up was 34 months, with 44% of patients having a longer follow-up of ≥3 years. Overall, the alirocumab group had a 15% reduction (HR 0.85, CI: 0.78-0.93; p=0.0003) of the primary composite endpoint (coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke, or hospitalisation for unstable angina) compared with the placebo group. All components of the primary endpoint were significantly reduced except death by CHD.

The absolute event rate of all-cause death was significantly reduced in the alirocumab group compared to the control group (3.5% vs. 4.1%, with an RRR of 15% [HR 0.85, 95% CI: 0.3-0.98; nominal p-value=0.026]), but was only informative due to predefined hierarchal testing. The number needed to treat (NNT) with alirocumab for the mean duration of 36 months was 64 for MACE and 163 for all-cause mortality. These numbers were much lower in the subgroup with an LDL above 100 mg/dL, reaching 29 for MACE and 60 for all-cause mortality. The entire benefit seems to be observed in this subgroup.

Both studies report an excellent safety profile with no signal alert, either for induced diabetes (as could be expected due to the drastic LDL reduction effect), or for cognitive dysfunction, or for haemorrhagic stroke or muscular outcome. Patients in the alirocumab group, as expected, reported more injection site reactions.

What have we learned from these trials and how will these data be translated into clinical practice?

THE CHEMICAL NATURE OF THE DRUGS MATTERS

Almost a year ago at ACC 2017, the SPIRE program was halted prematurely due to a lack of effect of another PCSK9 monoclonal antibody, bococizumab. Lack of clinical effect has been linked to a lack of reduction in plasmatic LDL levels, partly by the induction of antibodies against the drug which was not fully human[6].

COMPARATIVE ANALYSIS

Comparative analysis underlines that both molecules were tested in different secondary prevention settings (stable atherosclerotic patients versus early post-ACS patients), with different clinical characteristics profiles (e.g., previous MI was noted in 80% of patients in the FOURIER study versus 19% in the ODYSSEY Outcomes trial) with different strategies (one dose of evolocumab whatever the initial LDL level was versus two doses of alirocumab, with possible downgrading and even discontinuation of alirocumab for an LDL-C value <15 mg/dL) and timings (FOURIER expanded the number of patients recruited in a shorter time, thus being the first to release data but shortening the exposure to the drugs which probably made AMGEN miss the opportunity to show a benefit on mortality). Interestingly, in both studies a significant 25-27% reduction of ischaemic stroke was observed while one could have hypothesised that a strong reduction of LDL could have led to an increase in haemorrhagic strokes, as reported in SPARCL[7].

ANTI-PCSK9 EFFECTS ON CORONARY EVENTS

Regarding anti-PCSK9 effects on coronary events, evolocumab reduced the need for revascularisation procedures by 22% (HR 0.78, CI: 0.71-0.86; nominal p-value=0.01), either urgent (HR 0.73, CI: 0.64-0.83) or elective (HR 0.83, CI: 0.73-0.95). The predefined efficacy criteria of ischaemia-driven coronary revascularisation was also reduced in the alirocumab arm by 12% (HR 0.88, CI: 0.79-0.97; nominal p-value=0.009).

RISK/BENEFIT AND REIMBURSEMENT

The benefit/risk ratio is in favour of both alirocumab and evolocumab; however, randomised clinical trials lack sufficient power to detect rare adverse drug reactions. Only post-marketing studies and risk management appraisal by drug agencies will be able to identify midterm and long-term risk. The cost of this new class of lipid-lowering therapy (list price of more than US $14,000) is until now above what payers are ready to reimburse. If mortality data are able to convince the latter, a new type of negotiation could be initiated by focusing the drugs on a subset of patients as seen in ODYSSEY (ACS patients with uncontrolled LDL levels despite optimised lipid-lowering therapy). These trials will help to convince reluctant, sometimes suspicious physicians and patients about the LDL hypothesis and that lowering LDL is indeed so far the most powerful preventive action for the management of high-risk patients. Finally, from a methodological perspective, it will now be difficult to conduct trials without a PCSK9 inhibitor as comparator.

WHO CAN BENEFIT?

In view of the available evidence from these trials, patients who may benefit most from these new treatments seem to be high-risk, uncontrolled secondary prevention patients with an LDL-C above 100 mg/dl despite maximal tolerated high-dose statins and ezetimibe (due to the lower cost of this molecule), patients with

recurrent ischaemic events and no other modifiable factors, and patients with multivascular and/or polyvascular disease (especially PAD)[8].

Conclusion

In conclusion, the anti-PCSK9 antibodies represent a promising class, with proven clinical efficacy including total mortality reduction in ODYSSEY Outcomes, with no safety signals. Further analyses are warranted for better identification of high-risk patients who will benefit most from these efficient but expensive lipid-lowering molecules. Finding solutions to make this effective treatment available worldwide will be one of the main challenges of the cardiovascular community in the coming years.

Conflict of interest statement

P. Sabouret reports receiving consulting fees, lecture fees or funding for conference travel from Amgen, AstraZeneca, Bristol-Myers Squibb, Boerhinger, Novartis, MSD and Sanofi. A. Pathak reports receiving consulting fees, lecture fees, funding for conference travel or grants from Abbott, AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Menarini, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi, Servier and Takeda. D. Angoulvant reports receiving consulting fees, lecture fees or funding for conference travel from Amgen, AstraZeneca, Bayer, Eli Lilly, MSD, Novartis, and Pfizer.

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