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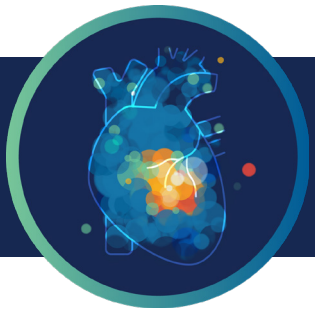
EXPERT INSIGHTS: Q&A WITH PROF. MACIEJ BANACH



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We now have an array of highly effective evidence-based lipid-lowering therapies at our disposal such as bempedoic acid, inclisiran and PCSK9 inhibitors. And with the oral CETP inhibitor obicetrapib demonstrating robust efficacy and a reassuringly strong safety profile in Phase 2 trials, with Phase 3 results eagerly awaited, is there a place for a gene editing agent such as VERVE-101 in the management of heterozygous familial hypercholesterolaemia?

Probably we should ask another question. What might be the place of CRISPR technology-based drug VERVE-101 in the lipid lowering pathway and management? Please notice that for many years we had only statins since 1990s, which were underused, and we did not clearly know how to use them effectively (in fact we still do not use them effectively). Then in 2002-2003, ezetimibe appeared, and after 2013 we started looking at the PCSK9 protein and possibilities of its effective inhibition. Obviously in the meantime bile acid sequestrants and niacin were also investigated but, in the end, they are almost not used. And now in 2024, we have not only those mentioned above, but also the combination of these drugs, bempedoic acid, first in class ACL inhibitor, new CETP inhibitor – obicetrapib, research on anti-PCSK9 vaccinations, soon oral PCSK9 inhibitors, etc. I am saying this, because we finally have an opportunity to individualize/personalize our lipid lowering therapy for different patients, not only taking into account the cardiovascular risk, but also concomitant disorders and in the consequence concomitant therapies (with the risk of drug-to drug interactions), patients' adherence to therapy and patients preferences, cost of the drugs and limitations associated with the reimbursement, possible drug-related side effects, etc. It means that now, and definitely in the very short future we have all the tools to have most of our patients at or near the LDL-C goal. I strongly believe, that also VERVE-101, assuming positive results of forthcoming studies, can only help in this regard.

Should the irreversibility of gene editing, changing the genome forever and the potential for off-target edits be a cause for concern or should we be embracing the ability of CRISPR-Cas9 technology to durably lower LDL-c for many years after just a single potentially therapeutic dose of VERVE-101?

For each new intervention, and also in case of CRISPR-Cas9 technology, we should not only focus on efficacy, which is quite predictable – taking into account lack of PCSK9 protein synthesis, but, especially now in the era of anti-science movements and denialists, we should also provide very clear data that the gene editing associated with the PCSK9 protein, which is irreversible, is simply safe. Knowing the mechanism of action and the role of PCSK9 protein, and the first human phase 1b study data that was presented at the AHA Congress in Philadelphia, with the patients that were followed up to 180 days, we may initially confirm this. Obviously further data with much longer follow-up are required to confirm this.

Two of the ten participants experienced serious cardiovascular events after receiving the investigational product in the heart-1 trial. Were these events simply a direct reflection of the high cardiovascular risk of the study participants?

This is indeed an important question on the obtained results that might be misinterpreted without suitable explanation. First, it is worth emphasizing that these two events, based on the opinion of the independent data and safety monitoring board were determined to be unrelated to treatment. Second, it needs to be emphasized that the enrolled patients were not only diagnosed with HeFH, but there were patients with advanced cardiovascular disease, with prior coronary revascularizations with either coronary artery bypass grafting or coronary stenting procedures or prior myocardial infarctions. In such a population the risk of recurrent cardiovascular disease (CVD) events, even with the optimal therapy, is increased. For example, in those patients presenting with acute coronary syndromes in Poland, even 1 in 5 patients (20%) can have another MI in the first 12 months. And third, in all patients treated with different lipid lowering therapies, but also in other patients with anti-hypertensive therapy, anti-diabetic therapy, we are not able to completely reduce the cardiovascular risk. Residual CVD risk is a fact, that is why we strongly emphasize to always try to reduce LDL-C with the approach of the lower the better for longer, and the earlier the better, but also look at other risk factors, like hypertension, diabetes, elevated levels of Lp(a), elevated hsCRP/IL-6, triglyceride rich lipoproteins, thrombotic factors, etc. We should probably also add therapy non-adherence, which is an independent risk factor of CVD events. Only then, with such a comprehensive approach to all (residual) CVD risk factors, we might ensure hypothetically optimal approach to CVD risk and effective prevention.

Is there an argument for suggesting that the study participants were not on optimal maximally tolerated lipid lowering therapy prior to enrolment into the heart-1 trial?

To answer this in a substantial way I need to see the final version of this paper published. Also considering the number of patients included in this phase 1b trial, I think it is too early to elucidate it. One thing however I would like to strongly emphasize, there will not ever be the therapy that completely prevents and stops atherosclerosis. Thus, even with such an effective therapy associated with the gene editing for PCSK9 protein, atherosclerosis might also progress if we have diabetes, obesity, hypertension, elevated levels of inflammatory biomarkers – when residual CVD risk exists, as I have emphasized above. Therefore optimal baseline therapy (always with suitable lifestyle changes) with such an innovative therapy approach, is just the solution that may effectively stop the atherosclerosis. Therefore if we would like to be effective, we cannot reduce statin dose (de-escalation, which applies to even 25% of physicians) when we add ezetimibe, and we cannot withdraw ezetimibe, when we add PCSK9 modulators (ezetimibe itself, based on the data from Odyssey APPRISE might increase the number of patients being on the LDL-C target by even 10-15%).

In plain language how would you summarise the key take home messages from the interim results of the heart-1 clinical trial to patients in your clinic?

The perspective lipid lowering therapy associated with the irreversibly gene editing drug, gene responsible for the cholesterol metabolism, associated with the PCSK9 protein, administered only once in the life course, was shown to be effective in the reduction of LDL cholesterol in a dose-dependent manner – so the higher dose, the higher reduction, with even up to 55% LDL cholesterol reduction. The hitherto results may also suggest that the treatment is safe, what supports further investigation of the drug, which might be, assuming further positive results, available for the patients in the next several years. This might change our approach on the effectiveness of atherosclerosis and atherosclerotic cardiovascular diseases therapy, among others in patients that cannot be treated effectively with existing lipid lowering therapies (due to adverse events, interactions, problems with compliance).

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