THE SYNERGISTIC CONTROL OF CHOLESTEROL FRACTIONS – INNOVATIVE CONCEPTS IN OUR PATIENTS

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Abstract
Lipid-lowering drugs reached a peak since large scale development of statins, which control well LDL-Cand HDL-C levels.Beyond this "state-of-the-pharma", recentresearch show that three are more efficient solutions. The dual clinical cases display distinct dyscolesterolaemic particularities which ask for innovative therapeutic solutions.The first clinical case is a 24 y. o. biomedical student, with severe coronary family history (a brother suddenly dead at the age of 28 y. o., father dead at 44 y. o. after the second MI), perfect preventive lifestyle, LDL-C 232 mg/dL, HDL-C 36 mg/dLandhs-CRP 3,6 mg/L. It was initiated a treatment with a redutable statin, in progressive dosages till the maximum one in the guidelines, LDL-C lowering to 202 mg/dL. Beyond statins, we can lower LDL-C more using PUFA and PCSK9 inhibitors.The second clinical case was a71 y. o. diabetic controlled by oral antidiabetics, with controlled hypertensionby ACE-inhibitors, LDL-C 65 mg/dL under statin. The subject presents with substernal pressure and emesis; an HDL-C value of 22 mg/mL and two tight stenoseson ACD segm. 1, and ADA segm. 2 are remarkable. Case interpretation: qualitative dimension – lowering HDL-C antioxidant capacity in acute coronary syndromes; quantitative dimension – low HDL-C remains a cardiovascular risk prediction in statin treated subjects. Beyond statins, we can increase more HDL-C using dalcetrapib, a CETP inhibitor. The drug classes proposed for these two patients are important pharmacologic tools in synergistic control of cholesterol fractions.

Keywords: LDL-C, HDL-C, statins, PCSK9-i's, CETP-i's

1. INTRODUCTION

State-of-the-lab. Even clinically discrete, the blood cholesterol became an important player in cardiovascular risk since the laboratory boom. The balance of cholesterol fractions, HDL-C – the good, and LDL-C – the bad, created the term dyslipidaemia/dyscholesterolaemia. More recently, the diabetologists were fascinated by this approach inventing the term dysglycaemia. As we talk about hypertension control when BP values decrease under 140/90 mm Hg, we can talk about dyscholesterolaemia control at LDL-C values under 100 or even under 70 mg/dL, according to risk, and HDL-C values over 60 mg/dL.

2. MATERIAL AND METHOD

State-of-the-pharma. Lipid lowering drugs, more precisely eulipemiants, even more accurately eucholesterolemiantsreached a peak since the large scale development of HMG-CoA-reductaseinhibitors (suffix statin), which controlswell LDL-C levels by reducingendogene cholesterol synthetisedat hepatic level. Ezetimibe, the prototype agent of exogene cholesterol loweringand fenofibrate, the prototype agent of blood triglycerides lowering are building, together with statin, a pharmacological triangle. Beyond this popular triad among practitioners, there are, according to recent trials, more efficient solutions for LDL-C lowering.
In contrast, the efforts made for raising HDL-C were not yet comparable with those for lowering LDL-C. This fact could be due to HDL-C heterogeneity, presenting many fractions, not all „good".
The eucholesterolemiant medication act not only at the proximal terminal of the Dzau-Braunwald continuum, on dyslipidaemia, but also at the more advanced level of myocardial infarction, where it produces the real cooling (measured by a thermistor) and figurate cooling (lowering inflammatory reaction) of atheroma plaque, lowering the risk of rupture. (Barter, 2007)

Lipid lowering drugsmainly represented by statins and fibrates,are part of a cardiovascular therapeutic building together with betablockers, nitrates, calcium channel blockers, diuretics, renin-angiotensin-aldosterone modulators, inotropic agents, antihypertensives (which may include some already mentioned drugs), antiarrhythmics, antithrombotics.
To underline the practical importance of the problem, we present two study cases with distinct dyscholesterolaemic features for any of both settings, for which we propose innovative therapeutic solutions.

3. RESULTS AND DISCUSSIONS

The first case study refers to pharmacologic agents used for lowering LDL-cholesterol ("bad" cholesterol). It actually enters the conceptual frame of optimizing familial hypercholesterolaemia (FH) treatment, with an accent over the role of emergent therapies for reaching the target levels in this disease.
FH is characterized by total cholesterol values of over 260 mg/dLin children, and > 290 mg/dLin adults. In this disease could also be observed tendon xanthoma, both in patients and in 1st and 2nd degree relatives. FH is strongly associated withpremature ischaemic heart disease and defectively presents several mutations of LDL-receptor, sometimes over 200. It appears more frequently among Latvian Jews, Lebanese Christians, French Canadians, Ashkenazi and Sephardic Jews. Heterozygot andhomozygot FH are considerably different in clinical terms.
M. S., a 24 years old biomedical student, with severe familial coronary history (a brother suddenly dead at the age of 28, father dead at 44 years old after the second myocardial infarction, uncle and grandfather dead under 50, unclear reasons), with a perfectly preventive lifestyle (no smoking, no alcohol, no drugs, daily physical exertion), never hospitalized, no diabetes or dysthyroidism, which presents a LDL-C value of 232 mg/dL, but also a HDL-C value of 36 mg/dLand hs-CRP 3,6 mg/L.
The LDL-C lifespan cummulative exposure concept and associate cardiovascular risk is, in normal individuals, clinically significant over the age of 60, in FH heterozygot form over 25 years old, and in homozygot form over 15 years old (on the absciseage in years, on the ordonatethe cummulative LDL-C exposure). (Figure 1) (Horton et al, 2009)

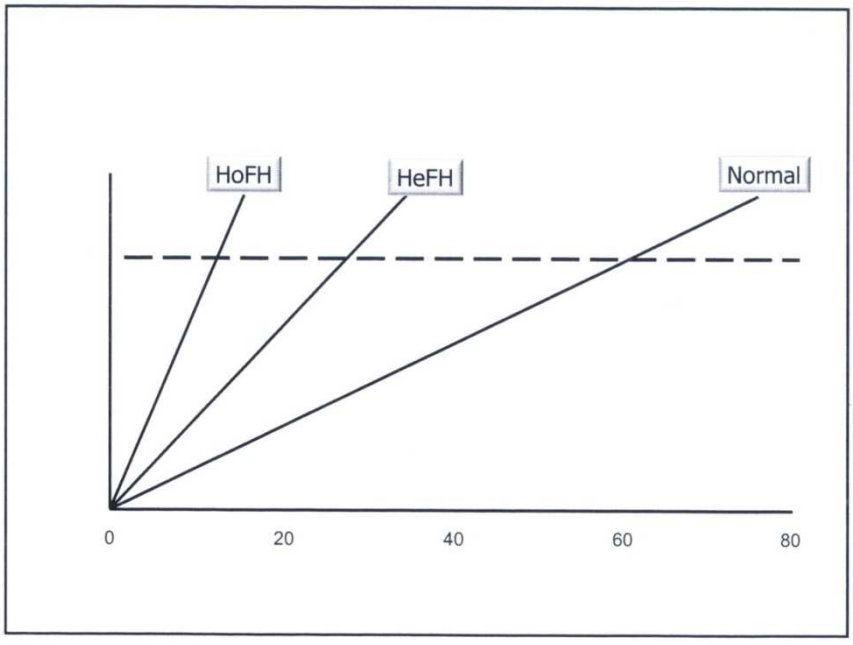

Figure 1.The LDL-C longlifecummulative exposure concept and associate cardiovascular risk

We have been initiated in this subject a pharmacological treatment with a redutable statin in progressive dosages till the maximum dosage in the guidelines, with LDL-C reaching 202

mg/dLafter six months of treatment. Statins efficiently lower hyper-LDL-cholesterolemiaat populational level; however, we observe a confined efficacy in FH.
The next step was to associate PUFA (PolyUnsaturated Fatty Acids). After other three months of combo treatment with statin maximal dosage +PUFA, LDL-C reached the level of 187 mg/dL.
Further, we associated a cholesterol absorption inhibitor, ezetimibe. After three months of triple combo, LDL-C stepped down to 158 mg/dL.
Due to low efficacy of current medication, we took into consideration more complex therapies, available in the USA, like:

- Bile acid sequestrants, with up-regulating effect at hepatic LDL-receptor level (such an effect is also present in statins and cholesterol absorption inhibitors)
- Antisense Oligonucleotides – Mipomersen
- Microsomal Triglyceride Transfer Protein Inhibitors – Lomitapide
- Monoclonal Antibodies adressing PCSK9. (Stein et al, 2012)
- Proprotein convertase subtilizin/kexin 9 bindsLDL-receptors, leading to their accelerated degradation and, subsequently, to LDL rise. (Maxwell et al, 2012)

Finally, this subject was enrolled in a four years programme with a PCSK9 inhibitor. After nine months of treatment, LDL-C reached the level of 133 mg/dL (interim result). The trend seem to be favourable, so we hope that, at a moment, LDL-C could decrease under the threshhold of 100 mg/dL.
The second study case refers to pharmacologic agents used for the HDL-cholesterol („good" cholesterol) increase. (Kaski JC, 2012)
HDL-C became o new goal in atherosclerotic disease, based on the following reasonsă:

- Firm epidemiological link with cardiovascular outcomes
- Exciting therapeutic opportunity
- HDL-C is a complex particle with multiple functions
- The first CETP inhibitor Torcetrapib causedincreased mortality in ILLUSTRATE trial
- Current clinical trials will define the clinical role of HDL-Craising (Davidson, 2011)

HDL-C promotes the reverse cholesterol transport and mediates the effects of endothelial protection.
Patient I. P. is a 71 years old diabetic controlled with oral antidiabetics, with stage I arterial hypertension controlled with an ACE-inhibitor, LDL-C being 65 mg/dL under statin. This subject presents with substernal pressure and emesis; we can remark a HDL-C level of 22 mg/mL and two tight stenoseson ACD segm. 1, and ADA segm. 2. (Figure 2)

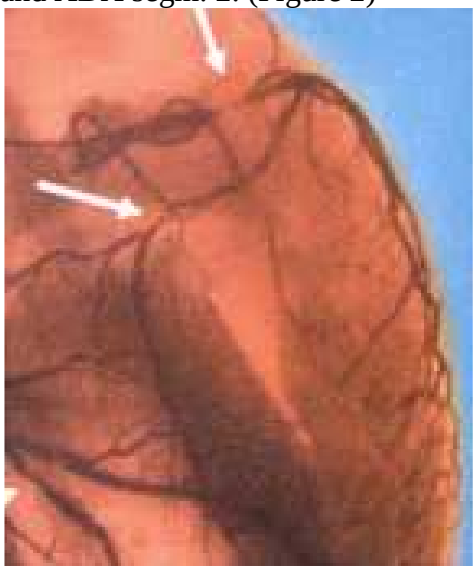

Figure 2. The coronary angiography of patient I. P.

Our case interpretation is bidimensional:

- qualitative – HDL-C anti-oxidative capacity reduction in acute coronary syndromes, and
- quantitative – low HDL-C level remains a predictor of cardiovascular risk in patients treated with statins. (Patel et al, 2011)

Because LDL-C is normal, we believe that low HDL-C is culprit of this evolution. So, we must find pharmacological solutionsto increase HDL-C level in patients already taking statin, likeour subjectI. P..

Among the three options: niacin, CETP inhibitorstype dalcetrapib or anacetrapib (not torcetrapib), therapies basedon apo-A1, the most attractive seems to be the second one.

The dal-VESSEL trial brings strong evidences supporting the use of dalcetrapib in our patient:

- it does not cause endothelial dysfunctionand does not influence the ambulatory blood pressure monitoring; so, this is a safe drug
- reducesCETP activitaty and increases the HDL-C level with 31% without affecting the NO-dependent endothelial function
- in contrast with torcetrapib, dalcetrapib does not increase blood pressure
- has a beneficial effect on vascular wall biology
- later test in dal-OUTCOMES trial

4. CONCLUSION

There are eight drug classes worldwide for dyslipidaemias control. According to contemporary academic sources, both important cholesterol fractions must be conveniently modulated in order to significantly reduce cardiovascular risk.The synergistic control of cholesterol fractions could be performed by using these new pharmacologic agents, eventually associated.

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