

‘Precision medicine’ and ischaemic heart disease: the stage is set for the new antibody based therapies (lipid lowering and anti-inflammatory)

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Improving cardiovascular risk assessment requires a ‘personalized’ approach. Appraisal of well-known cardiovascular risk factors should be integrated with markers of cardiovascular risk such as LDL cholesterol (C-LDL) and C-reactive protein (CRP). Results of the recent trials of PCSK9 inhibitor monoclonal antibodies open new interesting perspective. Data regarding the use of Evolocumab, in secondary prevention settings, in high-risk patients are very encouraging. In the same vein, the CANTOS study demonstrated, for the first time, that Canakinumab, an antibody with anti-inflammatory action (with no effects on C-LDL levels), decreases significantly the risk of major cardiovascular events in a high-risk population with elevated CRP and optimal C-LDL. This trial, for the first time, suggested a strategy distinguishing the anti-inflammatory from the cholesterol lowering component, thus differentiating the treatment. In the ensuing years, we will probably witness the clinical application of this concept.

Beyond the risk factors

Cardiovascular conditions continue to represent an important cause of morbidity and mortality and can affect patients without the risk factors described in the classical risk cards. A personalized approach implies, beyond the definition of the risk factors, the search for the so called markers of cardiovascular risk, such as LDL cholesterol (C-low density lipoprotein) and C-reactive protein (CRP), which better identify the presence and complexity of atherosclerotic lesions.¹ Furthermore imaging of atherosclerotic plaques and the study of their structure are important elements to consider in evaluating the individual risk both in primary and secondary prevention settings.^{2,3}

Treating high cholesterol

High cholesterol is an important risk factor, capable of initiate and promote the progression of atherosclerosis. The marked reduction of C-LDL, afforded by the use of powerful

statins, can stabilize atherosclerotic lipid plaques, thus rendering them less ‘vulnerable’.⁴ Notwithstanding the efficacy of statins in ameliorating the prognosis of patients affected with ischaemic cardiomyopathy (decrease event recurrences and cardiovascular mortality), well established by numerous multicentre studies, their use is still controversial in the primary prevention settings, where the risk benefit ratio of the treatment is less secured.⁵ A systematic review of randomized studies utilizing statins in a primary prevention setting, demonstrate that these drugs didn’t significantly decrease total mortality.⁶

On the contrary in secondary prevention statins provide excellent results, thus encouraging their use with the goal of reaching a C-LDL level <70 mg/dL. To further support this concept, thought the years, an inverse correlation has been established between C-LDL levels and cardiovascular events, till the level of 60 mg/dL.^{7,8} More recently, with the introduction of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, the effective levels of C-LDL have been further reduced to below 50 mg/dL.⁹

Inflammation and atherosclerosis

It is well known that high levels of CRP are associated with increased number of cardiovascular adverse events. Furthermore, the negative impact of inflammation on the prognosis has been asserted also despite normal value of blood cholesterol.¹⁰

The JUPITER¹¹ (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study evaluated this aspect, clearly demonstrating that statin is effective also in patients with very low value of LDL, but with high CRP.

The JUPITER trial was certainly innovative, because was conceived as primary prevention study, which sole enrolment requisite was the presence of inflammatory state and normal cholesterol levels (LDL < 30 mg/dL and CRP > 2 mg/L), regardless the presence of cardiovascular risk factors. The use of Rosuvastatin 20 mg provided, compared with placebo, a significant reduction of hard endpoint (cardiovascular death, myocardial infarction, and stroke) (0.45 vs. 0.85% per year; $P < 0.00001$). Moreover, and in line with previous data, the incidence of the study primary endpoint (myocardial infarction, stroke, coronary revascularization, hospital admission for unstable angina, and cardiac death) in the placebo group was 1.36% event/year, similar to the incidence expected in patients at moderate-high risk according to ATP-III (Adult Treatment Panel III) criteria (event incidence 10-20% at 10 years), and with at least two classical cardiovascular risk factors.¹² This information supported the role of CRP in identifying patients at increased cardiovascular risk. An in depth analysis of the JUPITER study revealed that the major reduction of cardiovascular events was accomplished in the subgroup of patients simultaneously reaching a level of C-LDL < 70 mg/dL and a CRP < 1 mg/L, with a relative risk reduction of 80%.¹³ There was a clear synergic interaction between the lipid reduction and the anti-inflammatory action of the statins. The PROVE IT-TIMI¹⁴ (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction) confirmed the conclusion of the JUPITER study, but in a different patient's population: patients with acute coronary syndrome. Patients randomized to receive either Atorvastatin 80 mg or Pravastatin 40 mg has a significant reduction of mayor cardiovascular events both when C-LDL levels reached a level below 70 mg/dL or CRP < 2 mg/L (2.8 vs. 3.9 events/year, $P = 0.006$).

New drugs for personalized treatment

Recent studies clearly demonstrated that both hypercholesterolaemia and inflammation are markers well correlated with the prognosis of patients with or without evidence of coronary artery disease. The effectiveness of statin therapy, either as lipid lowering and anti-inflammatory, has been firmly established. The lack of selective drugs acting on hypercholesterolaemia or inflammation, has hindered the implementation of personalized therapeutic solutions. The discussion has been centred on the possible pleiotropic effect of the statins, assuming that a marked decrease of the cholesterol levels could also determine a reduction of inflammation. In the last 2 years,

the implementation of new therapies clarified some of these concepts, thus introducing the opportunity for personalized therapeutic approaches.

PCSK9 inhibitors

The PCSK9 inhibitors act on the proprotein convertase subtilisin/kexin type 9 which physiologic role is the degradation of hepatic receptors for C-LDL (LDL-R), thus facilitating their transfer towards the lysosomes where is digested. The use of PCSK9 inhibitors in secondary prevention is an example of how the new molecules are used according to a personalized approach, requiring the pinpointing of patients at high risk for cardiac events, such as those with familial hypercholesterolaemia.¹⁵

The FOURIER⁹ (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study, evaluated the role of Evolocumab in secondary prevention of patients at high risk for cardiovascular events. The double blind randomized trial enrolled 27 564 patients with previous myocardial infarction, ischaemic stroke, or symptomatic peripheral arterial disease and LDL > 70 mg/dL or non-HDL-C > 100 mg/dL on optimal statin treatment with Atorvastatin 20 or 40 mg/day. After 48 weeks Evolocumab afforded a 59% reduction of C-LDL when compared with placebo ($P < 0.001$). Confirming the data of previous studies, 42% of the patients achieved very low levels of LDL (< 25 mg/dL) without side effects. The use of Evolocumab was associated with 20% reduction of the secondary endpoint (cardiovascular death, stroke, myocardial infarction) [hazard ratio (HR) 0.80; 95% confidence interval 0.73-0.88; $P < 0.001$].

Antibody based therapy with Canakinumab

Whether there is a clear evidence that statin treatment improve the prognosis of patients with elevated inflammation indices and normal cholesterol levels, the role of solely anti-inflammatory drugs has been unproven.

The recent publication of the CANTOS¹⁶ (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) study, using Canakinumab, a monoclonal antibody in use for some time in rheumatology, and acting on interleukin 1 β , addressed this specific question: the compound, in fact, has an anti-inflammatory action without affecting C-LDL levels. The study included 10 061 patients with previous myocardial infarction and increased levels of high sensitivity CRP, randomized to receive Canakinumab (50 mg, 150 mg, or 300 mg given subcutaneously every 3 months) or placebo. After 48 months, there was a marked reduction of the levels of CPR in the three groups receiving Canakinumab, without any effect on the lipid profile. The occurrence of the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) was significantly less for the Canakinumab treatment groups (HR of 0.93, 0.85, and 0.86 respectively for the doses of 50 mg, 150 mg, and 300 mg).

Of notice, the cardiovascular events often occurred in patients on placebo (more than 20% at five years), emphasizing that statins, to be fully effective, must afford control of the inflammatory process (CPR levels < 2 mg/L). The introduction of a solely anti-inflammatory drugs open an

interesting new chapter in prevention cardiology, prospecting the opportunity for personalized treatment, based on the levels of blood markers such as C-LDL and CRP.

New opportunity for personalized medicine

Precision medicine has become the staple of some medical subspecialties, namely oncology.

On the other hand some difficulties have been met in the field of cardiology.

Therapeutic solutions for ischaemic heart disease have been applied indiscriminately to all patients. For myocardial infarction, first thrombolysis and then primary angioplasty have been applied, regardless the pathophysiology, aiming at thrombus removal, which is the common final event of a series of variable circumstances. Similarly, secondary prevention of ischaemic heart disease utilized aspirin and lipid lowering drugs in all patients, and the results are clearly gratifying.

Nonetheless is fair to ask some questions: should the effectiveness of the lipid lowering treatment be measured in every patient as the threshold value for LDL of 70 mg/dL is reached, as suggested by current guidelines? Or are we better off modulating the type, the dosage, and the combination therapy, reserving a more aggressive approach only for patients with increased clinical risk?

In choosing a personalized lipid lowering therapy, which parameters should be contemplated suggesting an increased clinical risk?

Lastly, is it possible to quantify the inflammatory state, and directing anti-inflammatory treatment to patients with elevated CRP?

Recent trials studying the new antibody molecules^{9,16} open new perspectives, demonstrating that the use of powerful statins for all patients, aiming at reaching the recommended (European Guidelines) LDL level below 70 mg/dL, is probably in need for some rethinking.¹⁷ In all likelihood, according to the FOURIER study, the target C-LDL value will be lower than that recommended by present guidelines, even though, at present, a widespread use of PCSK9 inhibitors is untenable, mainly for economic reasons.

It is certainly thought-provoking separating the inflammatory component from the cholesterol levels, thus differentiating the treatment, as suggested for the first time by the CANTOS study. More time is necessary for the clinical application of this concept, and, likewise, economical issue will be important.

Envisioning future scenarios, it is reasonable to foresee a therapeutic strategy considering characterization of atherosclerosis by imaging technique, integrating the clinical stratification (risk factors) and blood markers, thus introducing an important third element.²

Conflict of interest: none declared.

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