Prevention challenges: The era of atherosclerosis regression

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Statins slow atherosclerosis progression and can even induce atherosclerosis regression. The reduction of cardiovascular events with statins by approximately one-third demonstrates not only their clinical efficacy but also the unmet clinical need. The aging of the population and the epidemics of the metabolic syndrome and diabetes contribute to the increasing burden of atherosclerosis in society, and fuel the need for novel complementary therapies to further improve clinical outcomes. Some targets, such as acyl-coenzyme A:cholesterol acyltransferase inhibition, have yielded disappointing clinical results. In contrast, there is strong evidence linking lower high density lipoprotein (HDL) cholesterol levels and greater cardiovascular risk, thus providing the rationale for targeting HDL in the prevention and treatment of cardiovascular diseases. Therapeutic approaches include direct infusions of HDL cholesterol or HDL-mimetic agents, as well as the inhibition of cholesteryl ester transfer protein (CETP). CETP inhibition appears to be one particularly promising strategy. The CETP inhibitor torcetrapib increases plasma HDL cholesterol levels by 40% to 60%, while modestly decreasing low density lipoprotein (LDL) cholesterol. Combining the HDL cholesterol-elevating properties of a CETP inhibitor with the LDL cholesterol-lowering properties of a statin may offer improved outcomes over targeting LDL cholesterol alone. This hypothesis is being extensively evaluated in a comprehensive program that involves several imaging studies and a large-scale clinical end point trial. The additional cardiovascular protection required for patients with atherosclerosis or risk equivalents will likely be provided by therapies that go beyond LDL reduction.

Key Words: Atherosclerosis; Cholesteryl ester transfer protein; HDL cholesterol; Intravascular ultrasound

Elevated low density lipoprotein (LDL) cholesterol is a strong independent risk factor for cardiovascular disease (1). Several studies (2-6) have demonstrated that statins have allowed us to enter the era of atherosclerosis regression. Indeed, 12 months of treatment with simvastatin has been shown to result in a reduced coronary atheroma volume, as assessed by intravascular ultrasound (2). Similarly, reductions in total atheroma volume on intravascular ultrasound were observed in the placebo arms of other intravascular ultrasound studies, such as the Avasimibe and Progression of Lesions on UltraSound (A-PLUS) (3) and acyl-coenzyme A:cholesterol acyltransferase (ACAT) IntraVascular Atherosclerosis Treatment Evaluation (ACTIVATE) trials (4), in which the vast majority of patients were treated with statins (mean LDL cholesterol

Les défis de la prévention à l'ère de la régression de l'athérosclérose

Les statines ralentissent la progression de l'athérosclérose et peuvent même induire sa régression. La réduction de près du tiers du nombre d'accidents cardiovasculaires au moyen des statines illustre non seulement leur efficacité clinique mais également un besoin clinique non comblé. Le vieillissement de la population et l'épidémie de syndrome métabolique et de diabète contribuent à alourdir le fardeau imposé par l'athérosclérose à la société et justifient le recours à de nouveaux traitements complémentaires pour améliorer encore les résultats cliniques. Certaines cibles, comme l'inhibition de l'acyl-coenzyme A:cholestérol-acyltransférase, ont donné des résultats cliniques décevants. En revanche, certaines preuves établissent un lien formel entre des taux de HDL-cholestérol bas et un risque cardiovasculaire plus grand. Ce qui justifie le ciblage du HDL-cholestérol dans la prévention et le traitement des maladies cardiovasculaires. Les approches thérapeutiques en ce sens incluent des perfusions directes de HDL-cholestérol et d'agents HDL-mimétiques, de même que l'inhibition de la protéine de transfert des esters de cholestérol (ou CETP pour *cholesteryl ester transfer protein*). L'inhibition de la CETP semble une stratégie particulièrement prometteuse. Le torcetrapib, un inhibiteur de la CETP, fait effectivement augmenter de 40 à 60 %, les taux plasmatiques de HDL-cholestérol tout en réduisant de manière modeste le LDL-cholestérol. En alliant un inhibiteur de la CETP, pour ses propriétés qui agissent à la hausse sur le HDL-cholestérol, et une statine, qui agit à la baisse sur le LDL-cholestérol, les résultats pourraient être plus satisfaisants qu'en ne ciblant que le LDL-cholestérol. Cette hypothèse fait l'objet d'études exhaustives dans le cadre d'un programme complet qui comprend notamment des examens d'imagerie et un essai de grande envergure reposant sur des paramètres cliniques. La protection cardiovasculaire additionnelle requise chez les patients athérosclérotiques ou présentant des facteurs de risque équivalents pourrait bien provenir de traitements qui agissent au-delà de la simple réduction du LDL-C.

values were less than 2.5 mmol/L during the study). Furthermore, regression of atherosclerosis was observed in both statin arms of the Reversing Atherosclerosis with Aggressive Lipid-lowering (REVERSAL) study (5) when assessing the subsegment with the largest disease burden, and the effect was significantly more marked in the more intensive lipid-lowering arm with 80 mg of atorvastatin (5). More recently, regression of atherosclerosis was also observed with 40 mg of rosuvastatin in A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden (ASTEROID) (6). However, the reduction of cardiovascular events by approximately one-third with statins have not only illustrated their efficacy but also the unmet medical need. Thus, a large number of atherosclerosis-related clinical events

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are not being prevented with current pharmacological approaches. In light of the aging of the population and the epidemics of the metabolic syndrome and diabetes, novel therapies, in addition to intensive statin treatment, are urgently required to further reduce the burden of atherosclerosis on the population.

CARDIOVASCULAR BENEFITS OF LDL CHOLESTEROL LOWERING WITH STATINS

Several large-scale, randomized, placebo-controlled clinical trials have demonstrated that LDL cholesterol lowering with statin therapy reduces morbidity and mortality in patients with or at risk of cardiovascular diseases (7-10). More recent active comparator statin trials have demonstrated that aggressive lowering of LDL cholesterol provides additional benefits over more moderate lowering. In the PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial (11), atorvastatin 80 mg brought about a significantly greater reduction in LDL cholesterol than pravastatin 40 mg (49% versus 21%, respectively, $P < 0.001$), and the values achieved with the treatments averaged 1.60 mmol/L and 2.46 mmol/L, respectively. In these patients with acute coronary syndromes, the risk of the composite primary end point (all-cause death, myocardial infarction, unstable angina requiring hospitalization, revascularization or stroke) was significantly ($P = 0.005$) reduced (relative risk reduction of 16%) by atorvastatin 80 mg compared with pravastatin 40 mg (11). Likewise, the risk of any component of the composite end point was also significantly reduced. The relative benefit emerged after 30 days of treatment, continued to the end of the study and was achieved without an excess of adverse events with the more aggressive therapy. Similarly, in the 10,001 patients with stable coronary artery disease followed for a median of 4.9 years in the Treating to New Targets (TNT) study (12), a reduction of LDL cholesterol levels to a mean of 2.0 mmol/L with atorvastatin 80 mg was associated with a 22% relative reduction in the risk of major cardiovascular events compared with a reduction of LDL cholesterol levels to a mean of 2.6 mmol/L with atorvastatin 10 mg ($P < 0.001$). The results of the Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) trial (13), conducted in 8888 patients, were similar to those of the TNT study, with atorvastatin 80 mg providing greater clinical benefits compared with simvastatin 20 mg. However, there was no difference between groups in total and noncardiovascular mortality in the IDEAL trial (13).

ACYL-COENZYME A:CHOLESTEROL ACYLTRANSFERASE INHIBITORS

The inhibition of the enzyme ACAT leads to reduced cholesterol esterification and has been a promising therapy for atherosclerosis (14). In theory, the inhibition of ACAT-1 may prevent the transformation of macrophages into foam cells in the arterial wall, and the inhibition of ACAT-2 in the liver and intestine may reduce serum lipids (15). The demonstration that ACAT inhibitors lower lipids and reduce plaque burden in animal models provided hope that these results would also be obtained in clinical trials. However, the results of two clinical trials (3,4) that evaluated ACAT inhibitors were disappointing. In the A-PLUS trial (3), intravascular ultrasound showed that there were trends for an increase in atherosclerotic burden in patients taking the ACAT inhibitor avasimibe. It is noteworthy that the mild increases in LDL cholesterol of 7.8%, 9.1% and 10.9% observed in the avasimibe 50 mg, 250 mg and

750 mg groups were paralleled with trends for mean increases in per cent obstructive volume on intravascular ultrasound of 0.7%, 0.8% and 1.0%, respectively. Whether these parallel changes were causally associated is unknown. However, these results underscore the potential importance of even small changes in LDL cholesterol in patients with coronary artery disease, as well as the potential detrimental effects of increases in unesterified cholesterol in the arterial wall associated with ACAT inhibition. Indeed, the paradoxical increase in atherosclerosis previously observed in mice lacking macrophage ACAT-1 may explain the findings of the A-PLUS trial (16).

Similar results were then obtained with a second ACAT inhibitor, pactimibe, in the ACTIVATE trial, which also did not meet the primary intravascular ultrasound end point (4). In addition, both secondary end points showed a less favourable outcome (attenuation in the degree of atherosclerosis regression) with pactimibe than with placebo. The change in total atheroma volume was -5.6 mm^3 with placebo and -1.3 mm^3 with pactimibe. Collectively, the results of the A-PLUS and ACTIVATE trials suggest that ACAT inhibitors will not translate into clinical benefits for patients with coronary artery disease.

CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

There is much epidemiological and experimental evidence supporting an inverse relationship between high density lipoprotein (HDL) cholesterol values and cardiovascular diseases (17), providing a strong rationale for elevating HDL cholesterol levels as a therapeutic strategy. Aside from being involved in reverse cholesterol transport, HDL is also thought to protect against atherosclerosis via a spectrum of well-documented anti-oxidative, anti-inflammatory, antithrombotic and antiapoptotic effects (18,19). The infusion of HDL had highly promising effects on atherosclerosis in animal models (20). In a randomized, placebo-controlled, double-blind clinical trial of patients with acute coronary syndromes, treatment with five weekly infusions of complexes of recombinant apolipoprotein A-1 Milano and phospholipids was associated with a mean reduction of 4.2% in atheroma volume measured with intravascular ultrasound after six weeks (21). Although the changes in atheroma burden at follow-up were significant versus baseline, the results were not statistically different from those in the placebo arm because only 47 patients were evaluated with intravascular ultrasound in this study. Nevertheless, these preclinical and clinical results support wider-scale assessment of HDL infusions and of other HDL-based approaches to induce regression of atherosclerosis in coronary arteries. In addition, the rapid changes in atheroma burden suggest that atherosclerosis may be a much more dynamic disease than previously believed.

The blockade of cholesteryl ester transfer protein (CETP) is another potential strategy for increasing HDL cholesterol (22). CETP is a hydrophobic plasma glycoprotein that mediates the transfer of cholesteryl esters from HDL particles to lower density lipoproteins. The potentially antiatherogenic effects of CETP inhibition include an increase in reverse cholesterol transport, an increase in HDL cholesterol levels and a decrease in LDL cholesterol (23). While the role of CETP in lipoprotein metabolism and atherogenesis is complex, there is growing evidence from genetic and animal studies to support the concept of CETP inhibition as a valid therapeutic approach for the

prevention and treatment of atherosclerosis (24). Torcetrapib has been shown to increase HDL cholesterol and significantly reduce atherosclerosis in a study of New Zealand white rabbits fed a high cholesterol diet (25). Relative to control animals, torcetrapib-treated rabbits exhibited substantial elevations in HDL cholesterol (5.45 ± 0.84 mmol/L versus 1.50 ± 0.16 mmol/L, respectively) and a 60% reduction in the extent of atherosclerosis in the aorta. In this preclinical study, the reduction of aortic atherosclerosis was found to be significantly associated with elevated levels of HDL cholesterol. A recent clinical study showed that the CETP inhibitor torcetrapib increased HDL cholesterol levels by approximately 40% to 60% in patients (26).

The next step is to determine whether the results obtained thus far with CETP inhibition can translate into atherosclerosis regression and greater reductions in clinical events than those obtained with statin therapy alone. Furthermore, it is hoped that ongoing studies in patients receiving torcetrapib and atorvastatin will help to establish a link between changes in plasma lipids (including HDL and the LDL to HDL ratio), plaque burden and clinical events. These objectives are the subject of several multinational, randomized, double-blind, placebo-controlled phase III trials. The Rating Atherosclerotic Disease change by Imaging with A New CETP inhibitor (RADIANCE) 1 and RADIANCE 2 studies (27,28) enrolled patients with heterozygous familial hypercholesterolemia and mixed dyslipidemia, respectively, and are assessing the effects of the combination of torcetrapib and atorvastatin compared with atorvastatin alone on carotid intima-media thickness, as assessed with B-mode ultrasonography. The Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) study (29) is assessing the effects of the same treatment regimens on atherosclerotic progression in coronary arteries in the largest intravascular ultrasound trial ever conducted. Finally, the Investigation of Lipid Level management to Understand its Impact IN ATtherosclerotic Events (ILLUMINATE) study is a large-scale cardiovascular end point trial that has randomly assigned 13,000 patients with coronary artery disease or risk equivalents to either combined torcetrapib and atorvastatin or atorvastatin alone.

OTHER PHARMACOLOGICAL AND NONPHARMACOLOGICAL APPROACHES

In addition to the therapeutic approaches aimed at raising HDL cholesterol levels, several novel agents target the inflammatory components of atherosclerosis and acute coronary syndromes with

the objective of reducing cardiovascular events. The Aggressive Reduction of Inflammation Stops Events (ARISE) trial is testing a synthetic antioxidant that is structurally related to probucol (30) in more than 6000 patients with recent acute coronary syndromes. In addition, several other anti-inflammatory compounds are being tested, including those that target the leukotriene pathway and phospholipase A2 and serine protease inhibitors (31-33). Because adipose tissue is an important source of proinflammatory mediators, the antiobesity agent rimonabant (34) can also be included in this category, and is being evaluated in imaging and clinical end-point trials.

Although novel pharmacological approaches bear potential to induce atherosclerosis regression and provide clinical benefits, several other important issues represent prevention challenges. While statins and antihypertensive drugs have been shown to reduce cardiovascular events in randomized clinical trials, the rates of nonadherence to therapy remain high in the clinical setting, thus limiting the real preventive impact of such medication. In addition, the development of powerful pharmacological agents is occurring paradoxically at a time when we are faced with alarming problems of detrimental eating habits and a lack of physical activity in our society. It is important that clinicians take the required time to discuss lifestyle changes with their patients, both in the primary and secondary prevention settings (35). The Lyon Diet Heart Study (36) provided very encouraging and provocative results, showing rapid and important reductions in recurrent cardiovascular events in men with previous myocardial infarction who were taught to eat fruits every day, more root and green vegetables, more fish, more bread and less meat (beef replaced by poultry), to replace butter and cream with canola margarine, and to use rapeseed and olive oils in food preparation.

CONCLUSIONS

While statins have allowed entry into the era of atherosclerosis regression, the health care system is confronted by a growing prevalence of cardiovascular disease and an expanding population at risk for future events. The additional cardiovascular protection needed for patients with atherosclerosis is likely to be based on novel therapies that are presently being evaluated and that go beyond LDL cholesterol reduction. The results of ongoing studies targeting HDL cholesterol will greatly enhance medical knowledge in the next few years and may provide further cardiovascular protection for patients with atherosclerosis or at risk for cardiovascular diseases.

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