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The Regression of Atherosclerosis: The Power of Multimodality Imaging

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Abstract

Coronary artery disease remains a leading cause of death in the Western world. It is well known that the reduction of cholesterol levels by statin therapy is associated with significant decreases in plaque burden. However, a critical question has been the ability of statin therapy to lead to lipid egress from plaque and subsequent plaque stabilization. This is crucial since lipid-rich coronary plaques are at increased risk for rupture and thrombus leading to events. We recently addressed this issue by conducting the YELLOW (reduction in yellow plaque by aggressive lipid-lowering therapy) trial. We reported that short-term intensive statin therapy reduces lipid content as assessed by near infrared spectroscopy (NIRS) in obstructive lesions. Histopathological studies suggest that the majority of acute coronary events are related to occlusive thrombus formation after disruption of a thin-cap fibroatheroma (TCFA) overlying a large necrotic lipid core. Optical coherence tomography (OCT) is an imaging modality with powerful resolution to allow for plaque characterization including the identification of TCFA. Yet, it still remains unknown as to the efficacy of high dose statin therapy for enhancing anatomic features of plaque stabilization. The YELLOW II Trial was therefore designed with the goal of combining the utilization of OCT and NIRS in the coronary arteries to extend our initial findings as well as link them to changes in plaque morphology with alterations in lipoprotein biology, HDL function and macrophage behaviour.

Keywords: Atherosclerosis; Regression; Optical coherence tomography; Near infrared spectroscopy

Introduction

Atherosclerosis is the number one cause of death in the Western world. It results from the interaction between modified lipoproteins and cells such as macrophages, dendritic cells (DCs), T cells, and other cellular elements present in the arterial wall. This inflammatory process leads to the development of complex lesions, or plaques, that protrude into the arterial lumen. Ultimately, plaque rupture and thrombosis can occur leading to the clinical complications of myocardial infarction or stroke [1,2]. Due to the prevalence of coronary artery disease (CAD), the regression of atherosclerosis has been a desirable clinical goal

Regression of Atherosclerosis-Preclinical Studies

The idea that human atheromata can regress at all is something that met considerable resistance over the years. The reason for this may have been that advanced atherosclerotic lesions in humans and in animal models contain calcification and fibrosis, characteristics that seem irreversible [3-5]. The first interventional study demonstrating substantial shrinkage of atherosclerotic lesions was performed in cholesterol-fed rabbits over 50 years ago [6]. Animals received intravenous bolus injections of phosphatidylcholine (PC), an agent that promotes cholesterol efflux from cells. After less than a week and a half of treatment, the remaining plaques were fewer and much smaller than initially with approximately 75% of the arterial cholesterol stores being removed. Using a variety of atherosclerotic animal models, other groups showed similar arterial benefits from the injection of dispersed phospholipids [7,8].

Armstrong and colleagues found that advanced arterial lesions in cholesterol-fed rhesus monkeys underwent shrinkage and remodeling during long-term follow-up after a switch to low-fat or linoleate-rich diets [9,10]. The subsequent regression period (lasted~40 months) resulted in the loss of approximately two-thirds of coronary artery cholesterol, substantial reduction in necrosis, improvement in extracellular lipid levels and fibrosis, as well as lesion shrinkage. Success in atherosclerosis regression was again achieved in rabbits in 1976, following reversion to a normal-chow diet in combination with the administration of hypolipidemic agents [11]. Decades later, a series of studies achieved shrinkage of atheromata in rabbits via injections of HDL or HDL-like apolipoprotein A-I (apoA-I) and PC disks [12]. Using a variety of mouse models of atherosclerosis, we and others extended these studies ultimately demonstrating that atherosclerosis regression is a coordinated process that involves lipid efflux factors such as HDL resulting in the emigration of foam cells out of plaques via chemokine receptor 7 (CCR7), a factor required for dendritic cell migration [13-25] (Figure 1). Interestingly, regardless of the animal model, one common theme seemed to be that regression was characterized by a decrease in plaque lipid content.

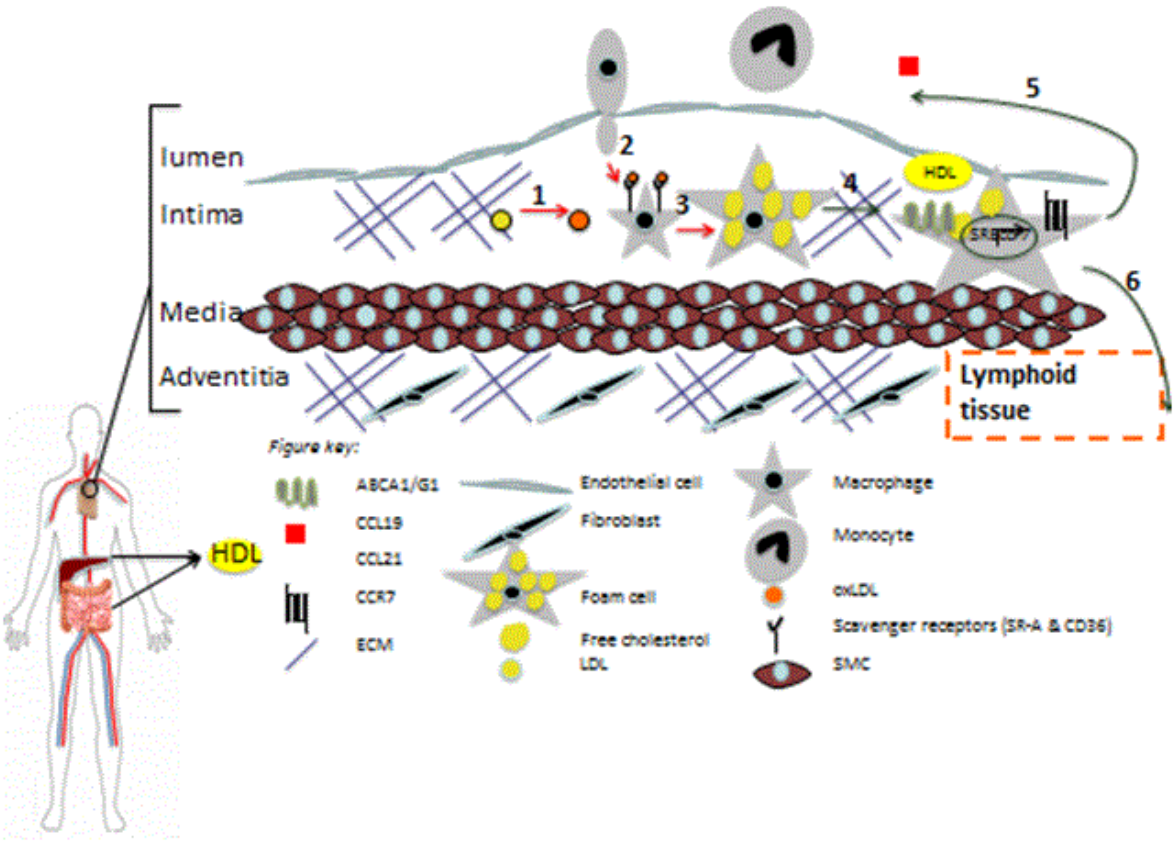

Figure 1: Regression of Atherosclerosis. 1) Oxidation 2) Diapedesis 3) Foam Cell formation 4) RCT 5-6) Macrophage Egress from Lesion to Lumen and Adventitia, respectively. HDL can inhibit processes 1-3 (red arrows) and promote 4-6 (green arrows). Macrophage egress can occur through the up-regulation of CCR7 via activation of the SREBP (sterol-response element binding protein) pathway. Figure adapted from Feig JE et al. Macrophages, dendritic cells, and regression of atherosclerosis. Front Physiol. 2012 Jul 18; 3:286.

Regression of Atherosclerosis-Clinical Studies

Although these published findings are exciting, the question remained as to whether regression can be detected in humans. It is well known that the reduction of cholesterol levels by statin therapy is associated with significant decreases in plaque burden. REVERSAL [26], ASTEROID [27], and more recently the SATURN [28] trial showed that in patients with CAD, lipid lowering with atorvastatin or rosuvastatin respectively reduced progression of coronary atherosclerosis, even causing plaque regression of some lesions.

Clinical events caused by CAD are related to plaque instability due to lipid content and activity within the plaque. With intravascular ultrasound (IVUS), it has been shown that long-term administration of high-dose statins can reduce atheroma volume by 0.99% to 1.2% in non-obstructive coronary lesions leading to a reduction in cardiovascular mortality [29]. Although reduction in atheroma volume has been most commonly reported, plaque composition likely plays a crucial role in the progression to the acute coronary syndrome [30,31]. In particular, lipid-rich fibroatheromas are at increased risk for plaque rupture and thrombosis [32,33]. Of all plaque components, the lipid core exhibits the highest thrombogenic activity [34]. Since the late stages of atherosclerosis promote thinning of the fibrous cap, early detection of high risk plaque eludes cardiac catheterization which provides only a two-dimensional image of the vessel lumen. Therefore, a significant coronary stenosis detected by angiography should be considered a marker for more diffuse, rather than isolated, atherosclerotic disease.

YELLOW Trial

Although high frequency IVUS provides some information about lesion calcification and degree of luminal obstruction, lipid content is not measured by conventional IVUS devices. As such, in studies aimed at detecting the effect of aggressive lipid-lowering using invasive coronary imaging such as in both REVERSAL [26] and SATURN [28], regression of atherosclerosis has been measured only by decrease in plaque area along the entire length of coronary artery. Though this provides a surrogate marker of atherosclerotic disease burden as a whole, it does not provide insight into stabilization of potentially high risk plaques, which is much more relevant to preventing acute coronary events. Despite these observations, the extent to which statins may modulate lipid content in severely obstructive coronary lesions remains unknown. Furthermore, possible changes in flow physiology have never been studied. Accordingly, we sought to

determine the impact of intensive statin therapy on the lipid content and flow physiology in patients with severely obstructive lesions, using diffuse reflectance near-infrared spectroscopy (NIRS) [32] and fractional flow reserve (FFR). A critical unanswered question has been the ability of statin therapy to lead to acute lipid removal from plaque and subsequent plaque stabilization. This represents a fundamental issue in cardiology because lipid-rich coronary plaques are at increased risk for rupture and thrombosis, leading to clinical events. Although high-dose statin therapy significantly reduces clinical events, whether or not these benefits are attributable to reductions in plaque lipid content, and the time needed to achieve these effects, remained to be elucidated. We addressed these issues in the prospective, randomized, YELLOW (Reduction in Yellow Plaque by Intensive Lipid Lowering Therapy) trial [35].

The application of NIRS to identify lipid deposition within coronary arteries has been validated *ex vivo* and *in vivo* [32-34,36-37]. Importantly, technological advances have now made it possible to combine IVUS and NIRS technology on a single instrument. This imaging catheter was recently used to successfully undertake the YELLOW study [35]. In brief, we enrolled a total of 87 patients with obstructive 2-3 vessel CAD. Following percutaneous coronary intervention (PCI) of 1-2 vessels, the diseased segment of the final diseased vessel was interrogated with FFR, IVUS and NIRS to assess plaque lipid content expressed as lipid core burden index (LCBI). Patients were then randomized to aggressive (rosuvastatin 40 mg daily) or standard of care lipid lowering therapy. All measurements, including FFR, IVUS and NIRS, were repeated at follow-up angiography at the time of staged PCI to the final diseased vessel. This carefully conducted study revealed that over a mean period of 7 weeks, median change in LCBI was significantly greater in the aggressive vs. standard group at both the lesion (-22.5 [-59.2, -3.5] vs. +8.0 [-7.7, 22.1]; p=0.005) and 4 mm max segment (-149.1 [-210.9, -42.9] vs. +2.4 [-36.1, 44.7]; p<0.001). There were no significant changes between groups in FFR or IVUS parameters from baseline to follow-up. The association between aggressive statin therapy and change in LCBI persisted after multivariable adjustment and remained consistent across numerous subgroups. These results enabled us to conclude that high-dose statin therapy significantly reduces lipid core content in hemodynamically significant coronary lesions within a short time. The findings also suggest that evaluating the response of lipid-rich plaques to therapy may provide a new risk-stratifying parameter in patients with obstructive CAD. In addition, further analysis has revealed that regression was significantly attenuated in the diabetic subgroup (Feig JE et al., accepted for presentation at Annual Society of Coronary Angiography and Intervention Meeting 2015).

YELLOW II Trial

Newer imaging modalities allow the opportunity to interrogate the high risk plaque in greater detail. Optical coherence tomography (OCT) provides high-resolution (~10 microns) cross-sectional images of plaque microarchitecture, with penetration depths approaching 2000 microns [38]. Second-generation frequency domain (FD) OCT has been used to image microstructural features including of the artery wall and correlates closely to histopathology. The detected microstructural features include identification of fibrous plaques, and lipid-rich plaques with high degrees of sensitivity and specificity [39-40]. Of critical importance, OCT's superior image resolution allows the accurate detection of thin cap fibroatheroma [30], which has been associated with cardiovascular outcomes [31]. However, it is important to note that OCT was not performed during the YELLOW study, therefore, only a very limited assessment of the effect of high-dose statin therapy on measures of plaque stabilization could be made.

The fundamental relationships between changes in plaque biology as defined by OCT and NIRS, have not been studied in the context of the biochemical effects of high dose statin therapy and therefore, we designed the YELLOW II trial. The effects of high dose statin therapy that remain un-investigated, but of critical importance, in plaque biology include changes in low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, apolipoprotein A1 (Apo-AI), and the qualitative effect of changes in the functionality of HDL and Apo-AI on macrophage activation, migration and inflammatory status. Therefore, we propose to image non-culprit coronary lesions with OCT and NIRS in patients with 2-3 diseased coronary vessels deemed to warrant intervention on clinical grounds. At the time of intervention, patients undergo PCI of the culprit lesion, and NIRS of the non-culprit lesion. If there is high baseline lipid content of the non-culprit lesion (max 4 mm LCBI>150), patients will be formally entered into this study. The final (non-culprit) lesion deemed in need of intervention will undergo staged intervention 8-12 weeks following the index procedure at which time this final lesion will be reimaged to determine whether high-dose statin therapy caused a reduction in lipid content as assessed by NIRS and altered plaque morphology by OCT. We are also profiling the relationship between plaque morphology by OCT and NIRS to changes in LDL, HDL, Apo-AI and macrophage functionality as a result of 8-12 weeks high-dose statin therapy. Taken together, combined utilization of OCT and NIRS applied in the coronary circulation, together with a comprehensive assessment of lipoprotein biology and inflammatory cell activity represents a powerful approach to addressing the systemic nature of vascular disease and the mechanisms of the efficacy of high-dose statin therapy for stabilizing atherosclerotic plaques.

Conclusion

The first YELLOW trial demonstrated that short term statin treatment leads to lipid regression as assessed by NIRS. We were unable, however, to extrapolate the effect on plaque characteristics as OCT was not employed. OCT is an intravascular imaging method that enables coronary artery plaque characterization by the highest achievable in vivo spatial resolution at 10-20 mm, a resolution of 10-fold higher than that of intravascular ultrasound (IVUS) [30,41]. A prior study has demonstrated OCT to be a reliable and accurate for characterization of high-risk plaque features, including thickness of fibrous cap and intraplaque lipid arcs [42]. In addition, macrophages can also be visualized by OCT and are seen as signal-rich, distinct, or confluent punctate regions that exceed the intensity of background speckle noise [41,43]. Most recently, Komukai et al. reported the benefits of atorvastatin on plaque characteristics using OCT [44]. Other studies have indeed demonstrated the power of multimodality imaging in various settings [45-47]. YELLOW II is a prospective study (Figure 2) designed to extend our understanding by assessing whether high dose statin therapy (rosuvastatin 40 mg daily) favourably alters plaque characteristics as well as linking these changes to increased HDL function and alterations in macrophage gene expression and behaviour.

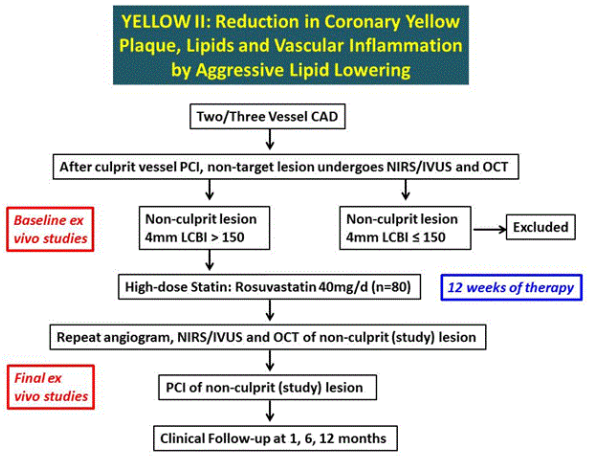

Figure 2: YELLOW II Clinical Trial Design.

The HDL hypothesis essentially states that a reduction of plasma HDL concentration may accelerate the development of atherosclerosis by impairing the clearance of cholesterol from the arterial wall. It implies that the efficiency of reverse cholesterol transport is partly dependent on the concentration of HDL and individuals with low HDL have a greater risk of CAD than individuals with high HDL levels. In a recent study, Voight et al. using Mendelian randomization tested the hypothesis that increased plasma HDL-C is protective for myocardial infarction (MI) by examining the relationship between genetic variations associated with elevated levels of plasma HDL-C and the risk of MI [48]. Interestingly, they found that some genetic mechanisms that raise plasma HDL-C do not necessarily lower the risk of MI and that these findings challenge the concept that raising of plasma HDL-C would uniformly translate into reductions in risk of myocardial infarction. This idea is consistent with recent studies in which the plasma level of HDL-C was raised pharmacologically (eg. AIM-HIGH [49], ILLUMINATE [50], dal-OUTCOMES [51-52], and HPS2-THRIVE [53]) without evidence that there were any reductions in cardiovascular events.

Although there are some who feel that the above data indicates that HDL should no longer be a therapeutic target, the above developments only emphasize that HDL biology is complex. In fact, they have led to a reshaping of the HDL hypothesis to focus on HDL function (i.e. efflux capacity). HDL cholesterol efflux capacity is a significant inverse predictor of coronary heart disease even after adjusting for HDL-C concentrations [54]. In other words, it is not HDL cholesterol itself that has a causal relation to atheroprotection, but rather HDL function, which cannot be reliably estimated through the simple measurement of HDL-C. This concept has recently been reinforced by a recent report that demonstrated that cholesterol efflux capacity was inversely associated with the incidence of cardiovascular events in a population-based cohort [55]. Based on all of the above, determining whether high dose statin can increase HDL functionality via macrophage cholesterol efflux assays is of clinical importance.

Through a variety of experiments, we have characterized the regressing plaque at the molecular level [25]. For example, we have reported that CCR7, a chemokine required for migration of monocyte derived cells and found to be functionally required for plaque regression (at least in murine models) plays a crucial role in promoting this process [15,19]. We have also demonstrated in murine models that one way to induce this gene is via lipid depletion [24]. The YELLOW II trial will be the first to our knowledge to determine whether these data can be extrapolated to a CAD population and how it relates to HDL function, alterations in macrophage gene expression, and plaque morphology.

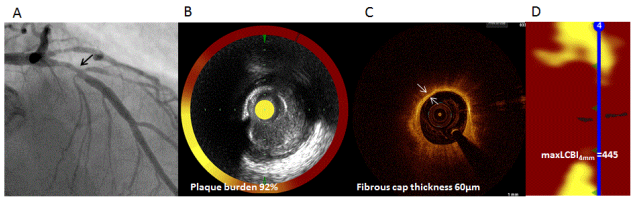

Figure 3: The Power of Multimodality Imaging. A) Angiogram of 59 year old patient presenting with unstable angina. Lesion (arrow) in LAD (left anterior descending artery) identified; B) Intravascular ultrasound (IVUS) of same segment demonstrates total plaque burden; C) Optical coherence tomography (OCT) reveals thin cap fibroatheroma (see arrows); D) Near infrared spectroscopy (NIRS) provides information regarding lipid content.

The idea that atheroma can regress is no longer a dream. Over the last few years, we and others have begun to dissect the molecular mechanisms of this process. We have discovered that decreasing the lipid content can directly lead to macrophage egress and plaque healing. The question however has remained as to how to translate these findings to the bedside. Therefore, imaging of the plaque in the patient has become a prime focus for investigators. Completion of the YELLOW II trial will further help us understand the interplay between plaque characteristics, lipid milieu, and reverse cholesterol transport. While tremendous progress has been made, our research serves as a reminder that angiography is simply luminography and it is features such as thin cap fibroatheroma and lipid burden, for example, that likely modulate the syndromes seen in clinical practice (Figure 3). On-going studies such as ours may provide novel pathways for diagnosis and therapy, with the ultimate goal of reducing the burden of cardiovascular disease.

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