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Research Paper

Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment

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ABSTRACT

Importance: Age-related macular degeneration (AMD) remains the leading cause of blindness in developed countries, and affects more than 150 million worldwide. Despite effective anti-angiogenic therapies for the less prevalent neovascular form of AMD, treatments are lacking for the more prevalent dry form. Similarities in risk factors and pathogenesis between AMD and atherosclerosis have led investigators to study the effects of statins on AMD incidence and progression with mixed results. A limitation of these studies has been the heterogeneity of AMD disease and the lack of standardization in statin dosage.
Objective: We were interested in studying the effects of high-dose statins, similar to those showing regression of atherosclerotic plaques, in AMD.
Design: Pilot multicenter open-label prospective clinical study of 26 patients with diagnosis of AMD and the presence of many large, soft drusenoid deposits. Patients received 80 mg of atorvastatin daily and were monitored at baseline and every 3 months with complete ophthalmologic exam, best corrected visual acuity (VA), fundus photographs, optical coherence tomography (OCT), and blood work (AST, ALT, CPK, total cholesterol, TSH, creatinine, as well as a pregnancy test for premenopausal women).
Results: Twenty-three subjects completed a minimum follow-up of 12 months. High-dose atorvastatin resulted in regression of drusen deposits associated with vision gain (+3.3 letters, $p = 0.06$) in 10 patients. No subjects progressed to advanced neovascular AMD.
Conclusions: High-dose statins may result in resolution of drusenoid pigment epithelial detachments (PEDs) and improvement in VA, without atrophy or neovascularization in a high-risk subgroup of AMD patients. Confirmation from larger studies is warranted.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the developed world (Miller, 2013; Wong et al., 2014). The non-neovascular or "dry" form accounts for 85% of all AMD and is characterized by accumulation of extracellular deposits, termed drusen (Sarks et al., 1994), between the basal lamina of retinal pigmented epithelium (RPE) and inner collagenous layer of Bruch's membrane (BM), which is the inner wall of the choroid. Progression to advanced AMD involves atrophy of the RPE and overlying photoreceptors (geographic atrophy), and/or choroidal neovascularization (neovascular or "wet" AMD). While there are effective anti-angiogenic therapies for the less prevalent neovascular AMD, there are no effective treatments for the more prevalent dry form (Miller, 2013).

Several clinical and epidemiological studies have established cardiovascular risk factors (including smoking, hypertension, and serum lipid status) to be associated with AMD development and progression, and both diseases share susceptibility genes (Miller, 2013; Yip et al., 2015; Tomany et al., 2004; Sene and Apte, 2014; Sene et al., 2015). This suggests that both diseases share similarities in their pathogenesis, and that interventions that reduce cardiovascular disease risk factors may be useful in AMD.

Bruch's membrane (BM) lies under the RPE and forms the inner margin of the choriocapillaris, and thus is considered the structural analog of the vascular intima (Curcio et al., 2001). Analogous aging changes in the vascular intima and BM are thought to relate to the pathogenesis of atherosclerosis and AMD, respectively (Sivaprasad et al., 2005). Similarities in the protein molecular composition of drusen and

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arteriosclerotic deposits corroborate this perception (Mullins et al., 2000). In both conditions, apolipoprotein B (apo B) and cholesterol accumulate, with subsequent modification, oxidation, and aggregation. Drusen components are derived from local tissues (retina/RPE secreting apo B,E-containing lipoproteins (Wang et al., 2009; Johnson et al., 2011)) and from the circulation (Curcio et al., 2011; Wu et al., 2010), and both AMD and atherosclerotic coronary artery disease involve lipoprotein retention. In AMD, an inflammatory response to the accumulated material may ensue with activation of complement and other components of the immune system, which can lead to atrophy of RPE cells and/or induction of a pro-angiogenic state and neovascular AMD.

Given these observations and similarities between atherosclerosis and AMD, it has been hypothesized that statin treatment may affect AMD status and/or progression (Hall et al., 2001). Statins suppress cholesterol synthesis by inhibiting HMG-CoA reductase (the enzyme catalyzing the rate limiting step in cholesterol biosynthesis). In addition, they increase liver LDL receptors levels (Bilheimer et al., 1983), reduce apo B synthesis (Arad et al., 1990) and suppress prenylation (the addition of hydrophobic molecules to a protein that is a physiologic process that control localization and function) (Kino et al., 2005). Multiple epidemiological studies have examined this relationship with conflicting data (Gehlbach et al., 2009). A 2015 Cochrane report (Gehlbach et al., 2015) concluded that "[evidence is] insufficient to conclude if statins have a role in preventing or delaying the onset or progression of AMD." A small, proof-of-concept, randomized, placebo-controlled study of the effect of simvastatin on the course of AMD was recently published, and suggested that simvastatin at 40 mg (equivalent to 20 mg atorvastatin) daily may slow progression of early/intermediate AMD, especially for those with the at-risk complement factor H (CFH) genotype CC (Y402H) (Guymer et al., 2013). Another recent study in patients with elevated plasma lipid levels found that statin use for more than a year was associated with an increased hazard for neovascular AMD (VanderBeek et al., 2013), and the authors postulated that these patients were resistant to statin treatment, rather than statins leading to increased risk for neovascular AMD. The Alienor study suggested that elderly patients with high HDL concentration may be at increased risk for AMD; furthermore, it found that HDL dysfunction might be implicated in AMD pathogenesis (Cougnard-Gregoire et al., 2014). In contrast, data from a recent meta-analysis of three population-based cohorts over a 20-year follow-up period did not show a significant association between lipid levels or lipid pathway genes with the incidence or progression of AMD (Klein et al., 2014a).

A major limitation in almost all studies thus far is the large heterogeneity of AMD disease (more than 100 at-risk genes and several phenotypes) (Miller, 2013; Fritsche et al., 2015) and lack of standardization in statin dosage (Gehlbach et al., 2009, 2015) or lipophilicity (Wu et al., 2010; Chitose et al., 2014; Fong, 2014). There is clear evidence from the cardiovascular literature that statin dose does matter (Cannon et al., 2004; Pitt et al., 1999). The PROVE-IT study (Khush and Waters, 2004) suggested that statin dose may be more important than LDL-c levels, whereas the REVERSAL and ASTEROID trials showed benefit of aggressive over moderate intensity/dosage therapy (Nissen, 2005; Nissen et al., 2006, 2004). The ASTEROID trial even showed regression of coronary atherosclerosis with very high-intensity statin therapy (Nissen et al., 2006). Similarly, Yu et al. showed that intensive but not regular-dose atorvastatin therapy resulted in regression of carotid atherosclerotic disease (Yu et al., 2007) and two magnetic resonance (MR) imaging studies have shown regression of the lipid core of atheromatous plaque after high-dose statin (Kramer et al., 2011; Zhao et al., 2011).

Here we present the first evidence that treatment with high dose atorvastatin may result in regression of drusen and improvement of visual acuity (VA) in patients with AMD with high-risk features for progression.

2. Methods

A case report and pilot multicenter phase1–2 prospective interventional study (Mass. Eye and Ear, Boston, United States, and University of Crete, Heraklion, Greece) were conducted with institutional review board (IRB) approval, and informed consent was obtained from all participants. Since there is some evidence in the literature that hydrophilic statins (such as pravastatin) may not be equivalent to hydrophobic statins (Wu et al., 2010; Chitose et al., 2014; Fong, 2014) we use the hydrophobic atorvastatin (80 mg, daily). Pilot study inclusions were as follows: patients over 50 years of age with diagnosis of AMD and the presence of many large (>300 μm in diameter and more than 100 μm in height) soft drusenoid PEDs. Exclusion criteria were as follows: presence (or history) of significant geographic atrophy or choroidal neovascularization in either eye; other eye diseases that could reduce VA (excluding mild cataract); history of eye surgery (other than cataract extraction); statin therapy (within the previous 2 years) at a dose equivalent to atorvastatin ≥40 mg; history of liver disease, rhabdomyolysis, or allergy to statins; pregnancy or nursing; current use of medications known to interact with statins (e.g., cyclosporine, systemic itraconazole, clarithromycin, HIV protease inhibitors); and elevated transaminases or creatine phosphokinase (CPK) at baseline. Pseudophakia was not a reason for exclusion, unless accompanied by significant posterior capsular opacity. Patients received 80 mg of atorvastatin daily. Baseline complete ophthalmologic exam, best-corrected VA by Early Treatment Diabetic Retinopathy Study (ETDRS) chart, fundus photographs, fundus autofluorescence, optical coherence tomography (OCT) and blood work (AST, ALT, CPK, total cholesterol, TSH, creatinine, as well as a pregnancy test for premenopausal women) were obtained. If there was any suspicion of occult neovascular AMD and FA and ICG were performed. Patients were monitored every 3 months with an eye exam, OCT imaging and AST, ALT, total cholesterol, and CPK monitoring. Best corrected VA acuity (EDTRS) and fundus photography were obtained every 6 months and at exit from the study. Duration of treatment was a minimum of 1 year. Physicians trained in internal medicine were involved in the design of the pilot study and in monitoring the patients during the study. Statistics were performed using GraphPad Statistical Software analysis (La Jolla, CA 92037 USA). The primary endpoint was reduction of drusenoid pigment epithelial detachment (PED) volume >50% based on OCT imaging at exit from the study. Drusen volume was measured by automated analysis of macular retinal pigment epithelium (RPE) elevations with the Cirrus HD-OCT. Any automated measurement can have artifacts in segmentation especially if the quality of OCT obtain is not adequate. All scans were verified that the segmentation was appropriate.

3. Results

3.1. Report of Initial Case

An otherwise healthy 63-year-old man with AMD on Age-Related Eye Disease Study (AREDS) vitamin supplements presented for a second opinion because of deteriorating VA. Baseline VA was 20/25 in each eye with significant distortion. Fundoscopy revealed bilateral extensive confluent large soft drusen and pigmentary alterations (Fig. 1, top row). Spectral domain OCT (SD-OCT) confirmed significant drusenoid PEDs as well as architectural distortion of the overlying RPE and photoreceptor layers (Fig. 2, top row). No subretinal or intraretinal fluid was present. Standard AREDS vitamin supplementation was continued. One year later, the patient became more symptomatic, and VA was slightly decreased to 20/30 in each eye. After extensive discussion, the patient was started on atorvastatin, beginning with 10 mg daily and increasing gradually over 9 months by a predetermined rate (two-month intervals of 10 mg/day, 20 mg/day, 40 mg/day, 60 mg/day, and 80 mg/day) to the target 80 mg daily dose. Six months after reaching a daily dose of 80 mg atorvastatin, VA improved by 12 letters to 20/20, and examination with fundus examination and SD-OCT revealing complete disappearance of the drusen without accompanying atrophy of the RPE. Intraretinal hyper-reflective foci remained (Figs. 1 and 2, bottom row).