Review Article

Statins for age related macular degeneration: promising but unproven

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Statins are used widely to treat hypercholesterolemia and atherosclerotic cardiovascular disease. They have inflammatory and immunomodulatory effects potentially useful for managing systemic autoimmune diseases such as rheumatoid arthritis, lupus erythematosus and multiple sclerosis. Statins also have anti-oxidative and large-vessel endothelial supportive properties that occur independent of their lipid-lowering effects. Additionally, statins can suppress macrophage and microglial activation responsible for initiating inflammatory cytokine release. More than forty percent of adults aged 65 years or older use statins in the United States and Australia, a prevalence that increases with age. The effects of statin usage on ophthalmic practice are probably underrecognized. Cardiovascular disease and age-related macular degeneration (AMD) share common risk factors, consistent with the "vascular model" of AMD pathogenesis that implicates impaired choroidal circulation in Bruch's membrane lipoprotein accumulation. AMD has a complex multifactorial pathogenesis involving oxidative stress, choroidal vascular dysfunction, dysregulated complement-cascade-mediated inflammation and pro-inflammatory and pro-angiogenic growth factors. Many of these components are hypothetically amenable to the primary (cholesterol lowering) and secondary (anti-inflammatory, anti-oxidative, anti-vasculopathy) effects of statin use. Experimental studies have been promising, epidemiological trails have produced conflicting results and three prospective clinical trials have been inconclusive at demonstrating the value of statin therapy for delaying or preventing AMD. Cumulative evidence to date has failed to prove conclusively that statins are beneficial for preventing or treating AMD.

Keywords: Age-related macular degeneration (AMD); inflammation; oxidative stress; atherosclerosis; statins

Received: 08 April 2021; Accepted: 04 June 2021; Published: 30 December 2021.

doi: 10.21037/aes-21-20

View this article at: https://dx.doi.org/10.21037/aes-21-20

Overview

Statins are widely used internationally to reduce the risk of cardiovascular diseases including atherosclerosis, cerebrovascular disease and peripheral vascular disease. In the United States and Australia, more than 40% of adults 65 years of age or older use statins (1,2). Thus, statins potentially affect the management of ocular diseases by intent (primary therapy: people not taking statins for systemic causes) or coincidence (secondary therapy: people taking statins for non-ocular disorders).

Statins are potent cholesterol-lowering agents with pleiotropic immune-modulating, anti-inflammatory and steroid-sparing properties (3,4). They have been used as adjunctive agents for the management of multiple sclerosis with interferon-β and for the treatment of systemic lupus erythematosus, rheumatoid arthritis and antiphospholipid syndrome (5). They reduce production of pro-inflammatory

cytokines in patients with systemic lupus erythematosus and vascular endothelial growth factor (VEGF) as well as tissue necrosis factor-α (TNF-α) in patients with antiphospholipid syndrome (5).

Satins also have anti-oxidative stress and vascular endothelial supportive properties at least in large blood vessels (6,7). The potential value of statins in preventing or managing age-related macular degeneration (AMD) has been studied extensively because inflammation, vasculopathy and oxidative stress are involved in the development and progression of AMD (8-11). Additionally, statins are useful for treating atherosclerosis which shares risk factors with AMD (9,11).

Statins and inflammation

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] have been used for decades to control blood cholesterol levels and reduce the risk of cardiovascular morbidity and mortality (4,12). Statins competitively block the active site of HMG-CoA reductase (4,5). This enzyme catalyses conversion of HMG-CoA to L-mevalonate, the precursor of farnesyl pyrophosphate (FPP) and its products in the L-mevalonate pathway including cholesterol and geranylgeranyl pyrophosphate (GGPP) (5,13). FPP and GGPP are non-steroidal isoprenoid compounds (4,5).

Inhibition of protein isoprenylation is largely responsible for statins' pleotropic effects beyond cholesterol lowering (4,5). Isoprenylation activates small guanine-triphosphate (GTP) binding proteins (Rho, Rac, Ras) regulating pro-atherogenic and pro-inflammatory pathways (4,5). These GTPases are involved in numerous cellular processes including gene transcription and adhesion and cell movement, division and signaling (14,15).

Statins' immunomodulatory effects have been documented in clinical trials showing that they reduce C-reactive protein (CRP, a biomarker of systemic inflammation) in normals and patients with hypercholesterolemia, independent of statin's cholesterol lowering effects (16,17). They have also been shown to increase immunosuppression and decrease rejection rates in cardiac transplant patients (18,19). Additionally, statins can suppress activation of macrophages and microglia responsible for initiating inflammatory cytokine release, reducing plasma TNF-α levels in SLE and antiphospholipid syndrome and VEGF in antiphospholipid syndrome (9,20-22).

Statins, vascular endothelial function and oxidative stress

Statins have been shown to support large blood vessel endothelial cells independent of their lipid-lowering effects (6,7). Improved endothelial cell function occurs before serum cholesterol decreases with statins, possibly by increasing production of endothelial-derived nitric oxide which inhibits atherogenesis (3,7). Additionally, statins may reduce vascular oxidative stress by inhibiting reactive oxygen species including superoxide and hydroxy radicals (3,6,7).

AMD pathogenesis

AMD is a complex multifactorial disorder affected by oxidative stress, choroidal vascular dysfunction, inflammation and epidemiological or environmental risk factors such as tobacco smoking and diet (8,10,23-25).

Geographic atrophy (GA) is an advanced form of non-neovascular (atrophic or "dry") AMD. Oxidative and other stressors of poorly-regenerative retinal pigment epithelium (RPE) cells cause intracellular lipofuscin and advanced glycation end product accumulation that stimulate inflammation via the complement cascade and additional pathways including the NLRP3 inflammasome (25,26). Age-related scleral rigidity has been suspected for decades of impairing choroidal circulation and contributing to lipoprotein accumulation in Bruch's membrane and AMD (27). This "vascular model" of AMD pathogenesis is consistent with the shared epidemiological risk factors of AMD and cardiovascular disease (27-29).

Inflammation is also involved in the development of neovascular (exudative or wet) AMD (26). Free radicals induced by oxidative stress enhance proinflammatory gene expression, further increasing oxidative stress in a potential amplification loop (23,26). Pathogen recognition receptors induce inflammatory cytokines and interferons formation including TNF-α and interleukin-1 involved in VEGF production (30,31). The "lipid wall" model of AMD proposes that RPE secretion of lipoproteins into Bruch Membrane forms a barrier that interacts with free radicals to promote macular neovascularization (MNV) (10).

Statins and AMD

Epidemiological and clinical studies have examined the

hypothetical benefits of statins' primary (cholesterol lowering) and secondary (anti-inflammatory, anti-oxidative, anti-vasculopathy) therapeutic effects in the management of AMD. A meta-analysis of 14 studies investigating the association between AMD and statin use found that statins were protective for early and exudative AMD but not geographic atrophy (32). In the Blue Mountains Eye Study, statins decreased the incidence of soft drusen but not early AMD (33). Statin use was not protective against AMD in several other large epidemiological studies including the Rotterdam (34), Beaver Dam (35), Women's Health Initiative Sight Examination (36) and Complications of Age-related Macular Degeneration (37) studies. Statin use was associated with a slightly increased risk of AMD in the Cardiovascular Health (38) and United Kingdom Health Improvement Network (39) studies. Statin use was also associated with progression of cortical and posterior subcapsular cataract formation and cataract surgery in the AREDS2 study (40).

Three prospective clinical trials examined the effect of statins on AMD. An early Italian study which randomized 30 participants to 20 mg simvastatin or placebo daily for three months found no visual acuity difference between the two groups at the study's end or 45 days afterward (11,41). A larger Australian "proof of concept" study which randomized 114 participants to 40 mg simvastatin or placebo daily for three years found that statins may slow progression to intermediate AMD, especially in people with the complement factor H at risk genotype (42). A multicenter non-randomized "pilot" study of 26 patients with drusenoid RPE detachments (PEDs) found that 80 mg of atorvastatin resolved RPE detachments and increased visual acuity (43).

Conclusions

Cumulative evidence to date has failed to prove conclusively that statins are beneficial for preventing or treating AMD. Convincing proof that statin therapy is useful for treating AMD patients will require very large, prospective, randomized studies that take into account the genetics and ethnicity of subjects (37). Such studies are becoming progressively more difficult to execute and less relevant clinically because of the high and growing prevalence of statin use in older adults (1,37).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Sayena Jabbehdari) for the series "Novel Treatment in Age-related Macular Degeneration" published in *Annals of Eye Science*. The article has undergone external peer review.

Peer Review File: Available at https://dx.doi.org/10.21037/aes-21-20

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/aes-21-20). The series "Novel Treatment in Age-related Macular Degeneration" was commissioned by the editorial office without any funding or sponsorship. MAM is a consultant for Ocular Instruments, Inc. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aes-21-20
Cite this article as: Mainster MA, Al-Janabi A, Moreno Andrade AB, Ledesma-Gil G. Statins for age related macular degeneration: promising but unproven. Ann Eye Sci 2021;6:34.