Review Article

Therapeutic Potential of Statins in Age-related Macular Degeneration

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ABSTRACT

Age-related macular degeneration (ARMD) is the leading cause of irreversible vision loss, affecting one in three people aged 75 and above. Although exciting new pharmaceuticals to treat ARMD such as endothelial growth factor (VEGF) inhibitors, are now available, they are effective only in selected group of patients, and can be used only during a narrow time window. Monthly intravitreal anti-VEGF injections with systemic exposure to anti-VEGF could be replaced by new drugs taken in a non-invasive way. Statins are the most commonly used lipid lowering drugs. The objective of this review is therefore to evaluate the evidence and discuss the rationale behind the recent suggestions that statins may be useful in the prevention and the treatment of age-related macular degeneration. This review recognised that there are potentially multiple biological bases for the protective effect of statins on the risk of ARMD. Thus, it is time to conduct a randomised controlled trial to provide direct evidence of the effectiveness of specific type statin in lowering the incidence and progression of ARMD. New intervention as statins usage to prevent the development of age-related macular degeneration and its progression remain an important strategy to limit the morbidity due to this significant public health problem.

Keywords: Age-related macular, Non-invasive treatment, Pleiotropic effects, Prevention, Statins

INTRODUCTION

Age-related macular degeneration (ARMD) is a progressive late onset disease affecting central vision. It is the leading cause of irreversible blindness among older adults, affecting one in three people aged 75 or older, and with the aging population the problem is increasing (Evans, 2001). Age-related macular degeneration is classified into two types: non-exudative or "dry', characterised by drusen and pigmentary changes, and exudative or "wet", characterised by choroidal neovascularisation (CNV) and eventually disciform scarring. Epidemiologic, genetic, and pathological evidences continue to accumulate, suggesting a possible link between risk factors for cardiovascular disease and age-related macular degeneration. Overlapping in risk factors for ARMD and cardiovascular disease has led to suggestion that the pathophysiology of these diseases have similar causal pathways (Snow and Seddon, 1999). Positive associations between ARMD and cardiovascular risk factors (blood pressure, plasma cholesterol, and smoking) lend support to this

proportion (Evans, 2001). The prominent histopathological and clinical lesions in ARMD involve Bruch's membrane, a specialised vascular intima separating the photoreceptors and their support cells, the retinal pigment epithelium (RPE). Because these lesions and Bruch's membrane contain abundant lipids, including cholesterol (Haimovici *et al.*, 2001; Curcio *et al.*, 2001), it is possible that ARMD and cardiovascular disease share common mechanisms at the level of the vessel wall.

However, there is no effective treatment for ARMD or for arresting its progression in its earliest phases. Current treatment options using endothelial growth factor (VEGF) inhibitors – anti-VEGF therapy are limited to the late stage of the disease, when central vision is already under great threat, and even new treatments make little impact on the rate of blindness. New drugs taken in a non-invasive way are being proposed to replace the monthly intravitreal anti-VEGF injections with systemic exposure to anti-VEGF.

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3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, generically termed statins are the most commonly used lipid lowering drugs. Recent experimental evidence suggests that these agents appear to display additional cholesterol independent or pleiotropic effects, contributing to prevention and inhibition of atherosclerosis. The statins' vascular pleiotropic effects include improvement of endothelial function, slowing the inflammation process, inhibition of the thrombus formation, enhancement of plaque stability and decreasing oxidative stress (Wolfovitz, 2005).

Statins are widely used in clinical practice because, they are effective and evidence based drugs. The Heart Protection Study randomised more than 20,000 patients, and the value of statins in reducing adverse cardiovascular events in high–risk patients, including the elderly, women, and even in those with low cholesterol levels was beyond doubt (Li and Hu, 2005). As a result, statins are now considered as one of the most powerful classes of agents for the treatment of vascular disease (Li, 2003; Ostadal et al., 2003). Statins are rapidly becoming frontline therapy among patients with diabetes mellitus, hypertension, and other known vascular risk factors. Statins lower serum lipid levels, and accumulation of lipids in the Bruch membrane and drusen is a key pathophysiologic pathway for ARMD development (Guymer et al., 2005).

Statins also appear to have beneficial effects on other ARMD pathways such as oxidative damage and inflammation (Guymer et al., 2005; 2008). Choroidal neovascular membranes associated with ARMD include macrophages (Grossniklaus, 2000), which may respond to statins. The objective of this review is thus to evaluate the evidence and discuss the rationale behind the recent suggestions that statins may be useful in the primary and secondary prevention and the treatment of age-related macular degeneration. Using the terms "Statins in age-related macular degeneration", the National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) was searched for relevant literature.

Statins and Incidence of Age-related Macular Degeneration

The association between the use of statins and age-related macular degeneration has been evaluated in many clinical studies; however the results have been contradictory. Klein et al. (2001) have an evaluated the impact of "lipid lowering agents" and Delcourt et al. (2001) evaluated "hypocholesterolaemic'' drugs and found no association with early ARMD or late ARMD. Thus the aggregation of statin and non-statin medications, as was probably done in these studies, would bias any association towards the null.

In 2005, Smeeth and others conducted a population based case control study consisting of 18007 people diagnosed with ARMD and control group of 86,169 people respectively matched on age, sex, and general practice (Smeeth et al., 2005). The crude odds ratio for the association between any recorded exposure to statins and ARMD was 1.32 (95% CI 1.17 to 1.48), but this reduced to 0.93 (95% CI 0.81 to 1.07, p=0.33) after adjustment for consultation rate, smoking, alcohol intake, body mass index, atherosclerotic disease, hyperlipidaemia, heart failure, diabetes mellitus, hypertension, use of other cardiovascular drugs, and use of fibrates. The authors stated that there was no evidence that the risk varied by dose of statin, duration of use, or that the risk varied for individual statins and concluded that in the short and medium term, statin use is not associated with a decreased risk of ARMD, and whether subgroups of patients with specific forms of ARMD (particularly choroidal neovascularisation) benefit from statin therapy remains a possibility.

Klein et al. (2007a) in an observational analysis of a randomized clinical trial found that the use of statins was not associated with ARMD. This study was limited to older females and the results could only be considered generalised to females from 63 year old and above. McGwin et al. (2006) evaluated both the use of cholesterol-lowering medications and statins specifically with regard to the risk of ARMD. A case-control study was conducted using data from the Cardiovascular Health Study of a population-based prospective study of adults enrolled in 1989 and 1990. The authors stated that no association exists between having used cholesterol-lowering medications and ARMD. However, there was a suggestion that statin use might increase the risk of ARMD. The results of this study should be interpreted in light of its limitations. Firstly, subjects with ARMD were not identified and not confirmed by a standardised comprehensive eye examination and the grading of fundus photographs. This limitation prohibits analyses with respect to disease severity and type.

Also, without confirmatory diagnostic information, there is also the possibility of misclassification with respect to ARMD status. Secondly, the study aggregated statins and non-statins into the group of cholesterol-lowering medications.

Data from large population-based studies, including previous analyses from the Blue Mountains and Beaver Dam studies, have not found a protective association between statin use and ARMD (Klein *et al.*, 2003). Some workers also stated that statin use is not reducing the risk for wet ARMD (van Leeuwen *et al.*, 2004; Kaiserman *et al.*, 2009). Absence of evidence is not evidence of absence. In another new analysis using data from the Beaver Dam Eye Study in Wisconsin, statin use at the 10-year examination was not associated with the subsequent incidence of early or late ARMD, or progression of ARMD at the 15-year examination (Klein *et al.*, 2007b). Data from case-control study also confirmed that use of statins was not associated with newly diagnosed exudative ARMD. The study had 80% statistical power to detect a protective effect of 0.70, but it cannot exclude a smaller effect (Klein *et al.*, 2007b).

Chuo *et al.* (2007) assessed the effect of lipid-lowering agents in the development of ARMD through a meta-analysis of observational studies. The pooled relative risk (RR) for all eight studies, and also for seven studies examining the use of statins, for those RR was 0.70 (95% CI, 0.48-1.03). The authors concluded that lipid-lowering agents, including statins, do not appear to lower the risk of developing ARMD, although clinically significant effects cannot be excluded. Hall *et al.* (2001) reported a significantly lower frequency of ARMD (defined broadly as all types and severities) among statin users relative to non-users. The OR reported in that study was 0.14, 95% CI 0.02-0.83. The limitations of the Hall's study (Hall *et al.*, 2001) have been addressed in detail and include the small sample size and the cross-sectional design (van Leeuwen *et al.*, 2001). Martin-Du Pan (2003) confirmed that statins are well tolerated and they could reduce the risk of macular degeneration. Data from cohort study of patients with bilaterial large drusen within a multicenter, randomised, clinical trial are not consistent with a strong protective effect (risk ratio, ≤ 0.85) of statins on the development of advanced AMRD among these patients (Maguire *et al.*, 2009).

Baghdasarian *et al.* (2004) in a cross-sectional analysis showed that ARMD was less common among statin users than nonusers (4% [1/27] vs. 22% [76/352]; p=0.02). Another observational study demonstrated a slightly higher risk of developing ARMD among statin users (Etminan *et al.*, 2008). Observational studies evaluating treatment effects are subject to range of biases due to heterogeneity of findings. Drobek-Slowik and colleagues case-control study revealed that statin use may be a protective factor against ARMD (Drobek-Slowik *et al.*, 2008).

Treatment indication and compliance biases, which refer to distortion of associations resulting from known and unknown differences in participant characteristics, prescribed treatment and treatment actually taken, are difficult to quantify and may also vary in magnitude between studies. However, there is evidence that the pattern, prescription, and type of statin usage have changed in the last decade. Furthermore, evidences have also indicated that not all statins are equally effective for lipid lowering. In a meta-analysis, atorvastatin displayed two to four times the potency of simvastatin in reducing total cholesterol levels (McCarty *et al.*, 2001). Thus, it is likely that the type and dosage of evaluated statins are different. Statins could provide some protective effect that is too small to be measured by small studies.

Recently, a large study conducted in a health organisation in Israel investigated statin use and the risk of age related macular degeneration and showed that the crude incidence rate of ARMD among patients at the lowest quintile of persistence with statins (7.18 per 1,000) was comparable to that of highest persistence quintile (7.13 per 1,000) (Shalev *et al.*, 2011). After adjustment for potential confounders, patients in the highest quintile of persistence with statins had a hazard ratio of 0.99 (95% Confidence interval: 0.78-1.26) for ARMD compared with patients in the lowest proportion of days covered (PDC) quintile. In addition to age, ARMD was found to associate with past smoking, asthma, diabetes and frequent visits to ophthalmologists or primary physicians prior to index date. The authors concluded and agreed with previous studies that showed no association between persistent use of statins and reduced risk of ARMD.

Statins in the Treatment of Age-related Macular Degeneration

The beneficial effect achieved by the treatment of endothelial dysfunction in chronic cardiovascular diseases is already presenting the basic treatment of the disease. Given the fact that the vascular system is uniform and physiologically and pathophysiologically consubstantial and in terms of therapy, it plays a key role in ARMD, endothelial dysfunction should be treated (Fisher, 2008; 2009). Self reported use of cholesterol lowering medications was associated with a four-fold decreased risk of ARMD progression in those who had ARMD at baseline (McCarty et al., 2001); however, because of small sample size, this finding was not statistically significant. The reliance on self reported information on statin use also represents a potential limitation of this study. McGwin et al. (2003) also reported a significant risk reduction for statin users (OR 0.30, 95% CI 0.20 - 0.45) and concluded that subjects with ARMD were significantly less likely to have filled a statin prescription.

The primary strength of this study was the use of the nested case-control design that allowed for the evaluation of statin use that occurred before ARMD diagnosis. Given the size of the study base, a large number of ARMD cases (550) and matched controls (5500) were identified thereby enhancing the statistical power of the study relative to other studies evaluating the relation between statin use and ARMD. This study had information on actual filled prescriptions and did not rely on self reported medication use compared with other studies (McGwin et al., 2003). Although, there is no information on whether the medications were actually taken, the succession of prescription refills during the observation periods among the majority of statin users suggests that these medications were actually being taken. Finally, this study population was limited to older males. Perhaps, the results should only be considered applicable to males aged 50 and above. Therefore, the results should be interpreted in light of its strengths and limitations of the study.

McGwin et al. (2005), in the case-control study of 871 ARMD cases and 11,717 controls after adjusting for the confounding influence of age, gender, and race, revealed a statistically significant relationship between ARMD and use of cholesterol-lowering medications (OR, 0.79; 95% CI, 0.63-0.99). The results of this study add to the growing body of evidence that cholesterol-lowering medications may reduce the risk of developing ARMD. In the analysis of the Blue Mountains Eye Study in Australia, while controlling for age and other factors, statin users at baseline and at the five-year follow-up had a 67% lowered risk of indistinct soft drusen, a key precursor lesion of late ARMD. Statin use, however, as stated by authors, was not related to the incidence of late ARMD or other early ARMD signs (Tan et al., 2007). This large population-based study as an observational study evaluating treatment effects is subject to a range of biases which were discussed earlier.

During a retrospective consecutive case series investigating the relationship between statin and aspirin use and the risk of choroidal neovascularization (CNV) in patients with ARMD, Wilson et al. compared the Age-related macular degeneration disease status and time of onset of CNV between patients treated or not treated with statins for at least 6 month (Wilson et al., 2004). Of CNV subjects, 20% used statins compared with 38% of dry ARMD subjects without geographic atrophy and 33% of controls with geographic atrophy (hazard ratio = 0.51, 95% confidence interval (CI) = 0.31-0.86, p=0.01). The general consensus is that therapy with statins or aspirin is significantly associated with decreased rates of CNV (Wilson et al., 2004; Girgis, 2004; Gaynes, 2004). The strength of this study (Wilson et al., 2004) is the used of main outcome measure, represented by angiographically evident CNV, and also the diagnosis, which was based on review of fundus photographs and fluorescein angiograms in masked fashion. The latest experimental study conducted by Sagara et al. (2007), evaluated the effect of specific statin-pitavastatin on CNV in rats and also recommended the use of pitavastatin in preventing CNV development in ARMD patients, based on claims that the therapeutic dose of pitavastatin for human hypocholesterolemia effectively suppressed experimental CNV in rats. The authors reported that pitavastatin-treated rats had significantly less fluorescein leakage, evaluated by masked observers; reduced thickness of CNV and decreased gene expression of VEGF. These encouraging results should be confirmed in clinical trials.

Schmeer et al. (2007) advocated for the use of statins in retinal eye diseases, based on their anti-apoptotic, anti-proliferative effects, besides lipid-lowering and anti-inflammatory properties. The authors presented evidence for the role of heat shock proteins (Hsps) as target of statin-mediated neuroprotective effects in ocular diseases.

The general consensus remains that a randomised trial of statin use in ARMD patients is warranted (Klein *et al.*, 2003; McGwin *et al.*, 2003; 2005; Wilson *et al.*, 2004; Chuo *et al.*, 2007; Wong and Rogers, 2007). Wong and Rogers (2007) also proposed the initiation of a randomised controlled trial. The authors estimated the required sample size, described clinically relevant endpoints, and concluded that only 1,704 participants may be needed for a five-year trial to evaluate the effects of statins on slowing ARMD progression by 25% or more (relative risks RR of 0.75 or lower), assuming a cumulative progression rate of 6% for the placebo group. Gehlbach and colleagues evaluated the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and/or progression of ARMD based on findings of randomised controlled trials (RCTs) (Gehlbach *et al.*, 2009). The authors stated that evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of age-related macular degeneration.

CONCLUSION

In conclusion, there are potentially multiple biological bases for the protective effect of statins on the risk of ARMD. With regard to the potential for a lipid lowering effect, cholesterol is a ubiquitous component of drusen in normal and ARMD eyes. With regard to pleiotropic effects, many of the same processes that occur in the atherosclerotic intima, probably also occur in ARMD. Neovascularisation is a major complication in both conditions. Therefore, angiogenesis remains potential point of statin modulation. Taken into account that not all statins are equally effective, the challenge for future laboratory research will be to determine the best type and dosage of statins and also to determine which processes are modulated by statins *in vivo* and therefore are primarily responsible for the apparent beneficial effects observed in previous studies. Clearly, further observational studies cannot adequately address many unanswered questions. It is time to conduct a randomised controlled trial to provide direct evidence of the effectiveness of specific type of statin in lowering the incidence and progression of ARMD. New intervention as statins usage to prevent the development of age-related macular degeneration and its progression remain an important strategy to limit the morbidity of this significant public health problem.

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