

## Abstract

Statins are known for their blood cholesterol lowering effect and are widely used in patients with cardiovascular and metabolic diseases. Research over the past three decades shows that statins have diverse effects on different pathophysiological pathways involved in angiogenesis, inflammation, apoptosis, and anti-oxidation, leading to new therapeutic options. Recently, statins have attracted considerable attention for their immunomodulatory effect. Since immune reactivity has been implicated in a number of retinal diseases such as uveitis, age related macular degeneration (AMD) and diabetic retinopathy, there is now a growing body of evidence supporting the beneficial effects of statins in these retinopathies. This review evaluates the relation between statins and the pathophysiological basis of these disease, focusing on their potential role in treatment.

Methods: a PubMed database search and literature review was conducted.

Results: Among AMD patient there is inconsistent evidence regarding protection against development of early AMD or delaying disease progression, though they have been found to reduce the risk of developing choroidal neovascular membranes (CNV). In patients with retinal vein occlusion there was no evidence to support a therapeutic benefit or a protective role of statins. In patients with diabetic retinopathy statins demonstrate a reduction in disease progression and improved resolution of diabetic macular oedema (DMO). Among patients with uveitis, statins have a protective effect by reducing the likelihood of uveitis development.

## Methodology

In August 2017 we performed a comprehensive literature review using the PubMed online database. We used the following terms ‘statins immunomodulatory effect’; ‘statins and retinal disease’; ‘statins and the eye’; ‘statins and age related macular degeneration’; ‘statins and AMD’; ‘statins and diabetic retinopathy’; ‘statins and retinal vein occlusion’; and ‘statins and uveitis’. We only included papers written in English. There were no date limits. We reviewed all articles and included those of interest focusing on animal models, laboratory research and clinical studies . We manually searched the reference lists of these manuscripts for additional studies.

## Introduction

### Background of statins

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have long been used for controlling blood cholesterol levels and reducing the risk of cardiovascular morbidity and mortality. While their mechanism of action in vascular disease is established, evidence is accumulating regarding alternative immunomodulatory roles that may enhance their cardiovascular effect as well as play a role in treating inflammatory diseases (1).

Statins were discovered in the early 1970s from *Penicillium citrinium* cultures (2). Further research showed that these molecules strongly inhibit the rate-limiting enzyme in cholesterol biosynthesis, HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to L-mevalonate and finally to farnesylpyrophosphate (FPP, the precursor for cholesterol synthesis) (3). Another product of the L-mevalonate pathway is geranylgeranylpyrophosphate (GGPP), which is synthesized from FPP. FPP and GGPP are both essential isoprenoids and serve as lipid attachments for various intracellular proteins that are thought to have an immunomodulatory effect by acting as adjuncts for different cell signaling processes, such as GTPases RAS, RAC and RHO (4).

Early evidence of the immunosuppressive effect of statins comes from studies on c-reactive protein (CRP), a systemic inflammatory biomarker, in patients following myocardial infarcts. Individuals with elevated serum CRP levels >3 mg/L have an increased risk of cardiovascular events and use of statins results in a reduction of CRP levels independent of their effect on blood cholesterol levels (5, 6). Endothelial function studies (7) as well as clinical trials from organ transplantation (8) and stroke prevention (9), support their additional immunomodulatory effect unrelated to lowering cholesterol. This has led to a recommendation to give cardiac transplant patients statins irrespective of their blood cholesterol levels (10) (1).

There is evidence supporting an inflammatory role in the pathophysiology of many retinal diseases and statins have been investigated in conditions such as cataract (11), glaucoma (12), diabetic retinopathy (13) and age-related macular degeneration (AMD) (14), with mixed results regarding their effect. There are also preliminary results suggesting it may reduce the extent of scarring following rhegmatogenous retinal detachment (15).

## Statin's immunomodulatory effect

The immunomodulatory effect of statins is exerted either directly on cells, such as interfering with T lymphocyte proliferation (16, 17), inhibiting the expression of co-stimulatory molecules CD80 and CD86 on B cells (REF) or through inhibition of cellular interactions and signaling molecules such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) (18), a potent pro-inflammatory cytokine that induces apoptosis of retinal cells (19). By influencing the cytokine balance from pro-inflammatory to anti-inflammatory, statins modulate the immune response and achieve an immunosuppressive effect (20) (21). Additionally, statins alter the interaction between the vascular endothelium and lymphocytes by blocking the intercellular adhesion molecule 1 (ICAM1) pathway, which facilitates transvascular migration of lymphocytes(22), thereby reducing the number of lymphocytes reaching the sites of inflammation. For a full description of statin immunomodulatory pathways please refer to figure 1.

## Age-Related Macular Degeneration

While the pathophysiology of AMD is not completely understood, there are well established risk factors, such as increasing age, smoking, genetic predisposition and increased body mass index (23). Pathological changes including lipid accumulation under Bruch's membrane, lipoprotein metabolism and inflammation, are thought to play a role in disease development and progression to its more advanced stages(24, 25). Drusen, the hallmark of early AMD are lipid-rich deposits located between the retinal pigment epithelium (RPE) and Bruch's membrane (26). The interaction between these lipids and reactive oxygen species results in the formation of peroxidised lipids that trigger local inflammation and destruction(REF),

which can either lead to the development of choroidal neovascularization (CNV) by releasing angiogenic cytokines or geographic atrophy by a direct toxic effect on the RPE cells (27). Several risk factors are shared for both cardiovascular disease and AMD, and serum levels for cardiovascular disease biomarkers (CRP and homocysteine) are significantly higher in AMD patients, suggesting similar pathophysiological processes such as chronic inflammation and atherosclerosis (29).

#### Statins in AMD

The potential role for statins in the management of AMD is supported through several pathophysiological mechanisms. Statins can preserve the vascular supply to the outer retina, by reducing atherosclerotic changes, thus maintaining the clearance of lipoproteins produced by the RPE and delaying the development of drusen. (30), (31) Their anti-inflammatory properties may further affect the inflammatory process underlying the development and progression of AMD,(32) and their effect on induction of heme oxygenase 1 and downregulation of LDL and peroxidised lipids,(34) may protect the outer retina, choroid, and RPE from oxidative damage (30). Lastly, statins' inhibit the activation of macrophages and the subsequent release of pro-inflammatory cytokines and matrix metalloproteinases (MMP 2), which are found in the CNV complex, delaying CNV development (30).

A meta-analysis of 15 studies examining the role of statins in AMD found a robust protective effect in early disease (35). They reduced the risk of early AMD by 17 %, whereas in late AMD their use was associated with a reduced risk of CNV development, but with no effect

on the development of geographic atrophy (GA). . The Blue Mountain Eye Study that followed 3654 people at 10 years intervals showed that statin users had a reduced risk of developing soft drusen, but did not affect the incidence of progressing to early AMD (38). This was replicated in the Beaver Dam Eye Study and the Rotterdam Eye Study, where no association was found between statin use and developing AMD at 5 years follow-up (39, 40). However, statin users in the Beaver Dam Eye Study were 32% less likely to develop soft indistinct drusen, 36% less likely to have large drusen ( $\geq 125 \mu\text{m}$ ) compared to non-statin users 71% less likely to present with late disease (39). In-line with these results, Maguire and colleagues examined 744 patients for the development of advanced AMD (GA or neovascularization) and found no protective effect for statins after 5 years follow-up (41). Several studies examined the effect of statins on development of disease specific features and progression to advanced disease. A cross-sectional study with a mean duration of statin intake of 61.1 months found that statins were associated with a lower risk of AMD in subjects  $\geq 68$  years old, which was more pronounced the longer statins were used (42). An open-label study examined the effect of high dose (80 mg) atorvastatin in patients with high risk features for progression to advanced AMD (presence of many large soft drusenoid deposits) and showed a trend towards reduced number of drusenoid RPE detachments and a visual gain of 3 letters on average after 1 year follow-up (14). Two randomised controlled trials aimed to accurately determine the effect of statins on AMD patients. The first examined the effect of 20 mg of simvastatin on 30 subjects for three months but did not show a statistically significant effect on vision (43). In the second study, 114 subjects were randomised to either 40 mg simvastatin or placebo. The results showed a four-fold decrement in the risk of disease progression in the treated group, and was even more prominent among patients with the complement factor H (CFH) allele (44), where the odds ratio for disease progression was 0.08. In 2015 a Cochrane systematic review and meta-analysis concluded

that there is inadequate evidence to support the role of statins in prevention or alteration of AMD progression (45). Tables 1 & 2 summarise the trials that offer support or do not for the protective role of statins in AMD .

## Diabetic Retinopathy

Diabetic retinopathy (DR) is a frequent complication of diabetes and increases in prevalence with disease duration. The most common causes of vision loss in diabetes are macular oedema and complications related to proliferative diabetic retinopathy. There is mounting evidence regarding endothelial dysfunction in diabetes and inflammatory processes leading to the development of DR (46). High glucose levels lead to activation of protein kinase C and induction of the aldose reductase pathway with overproduction of free radicals, endothelial cell injury and upregulation of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, ICAM1 and IL-6 (47, 48). This can lead to breakdown of the blood retinal barrier (BRB) resulting in loss of vascular integrity, which results in increased permeability, leading to macular oedema as well as compromised blood supply and retinal ischaemia. (49). More advance, proliferative diabetic retinopathy (PDR) is partly mediated by transforming growth factor  $\beta$ 2 (TGF  $\beta$ 2) which is up-regulated in diabetes. TGF  $\beta$  is responsible for the transformation of RPE and hyalocytes into myofibroblastic cells and induces contraction of fibrocellular complexes, which is related to developing vitreous haemorrhages and traction retinal detachment (50), resulting in vision loss. Hypercholesterolemia, in addition to hyperglycaemia, is regarded as a strong risk factor for endothelial dysfunction (51) leading to diabetic macular oedema (52). Total cholesterol and LDL were found to be significantly higher in subjects with clinically significant macular oedema (53)(54, 55) and were a significant risk factor for retinal hard exudate formation (55).

Statins have a role in maintaining the stability of the BRB by reducing reactive oxygen species, increasing nitrous oxide (NO) levels and increasing the numbers of endothelial progenitor cells (EPC), which are thought to play a role in maintaining a functional BRB. This results in improve blood flow velocity, reduce the vascular resistance and retinal perfusion of subjects with diabetic retinopathy (57, 58). Moreover, Atorvastatin was found to have pleiotropic functions on RPE cells including anti-proliferation, anti-contraction, and anti-adhesion (59). In PDR, statins are known to suppress TGF  $\beta$  and have been shown to suppress the formation of retinal neovascular tufts and delay the progression of PDR in animal models (60).

#### Statin clinical trials in diabetic retinopathy

The association between serum cholesterol and DR was first reported by Dornan et al (62). Extensive evidence linking elevated serum lipids and the increased risk of hard exudates comes from the early treatment diabetic retinopathy study (54) and the Wisconsin epidemiology study of diabetic retinopathy (63). High serum cholesterol levels were found to be a significant contributor to the extent of developing retinal hard exudates and patients with higher serum cholesterol levels at baseline had a 50% risk of vision loss compared to those with lower lipid levels (64) (55). The diabetic control and complication trial (65) showed that serum lipids, mainly the triglycerides to HDL ratio and LDL levels were risk factors for DMO and hard exudate formation. The study highlighted the potential role of lipid-lowering agents in reducing the risk of DMO. Furthermore, treatment with statins resulted in a reduction of the amount of lipids within the retina, seen on histopathological examination of



retinas from patients with high serum cholesterol and DMO (66). However, other studies looking at the total cholesterol level as a risk factor for developing DR were less conclusive (67). While the Chennai urban rural epidemiology study (68) found total cholesterol to be an independent risk factor for the development of DR, cholesterol was found to have a protective effect in the Singapore Malay eye study (69). In yet another study, blood triglyceride and LDL cholesterol levels were significantly associated with DR and diabetic macular oedema (DMO) respectively (70).

Statins and other lipid lowering drugs have been extensively studied as treatments for diabetic retinopathy. A study on the use of pravastatin demonstrated a reduction in hard exudates in all patients and reduced numbers of microaneurysms in 67% of patients. (71) Simvastatin 20mg was reported to delay the progression of DR and prevent the development of vision compared with placebo treated controls. (72) Similarly, treatment with atorvastatin resulted in a 66% reduction in hard exudates and leakage on fluorescein angiography among eyes with DMO and dislipidemia (74). However, it was not found to be beneficial in DR in 30 diabetic subjects with normal serum lipid levels (75). The combination of atorvastatin and fibrates demonstrated a significant reduction in macular oedema in 47 diabetic patients with non-proliferative DR (76), as well as reducing the rate of recurrent vitreous haemorrhage in eyes with PDR. (77)

Two randomised controlled trials, the fenofibrate intervention and event lowering in diabetes (FIELD) and action to control cardiovascular risk in diabetes (ACCORD) examined the effect of fenofibrate, a non-statin drug that reduces triglycerides and LDL cholesterol, alone or together with simvastatin respectively. In both studies, over 5 years follow-up a significantly positive effect was found in reducing DR progression and the addition of

simvastatin augmented the control of the DR (78-80). This led to less need for other treatment measures, such as focal laser in the FIELD study . These effects were cholesterol independent and may be attributed to anti-inflammatory, anti-apoptotic and vasodilatory effects which are NO mediated (81, 82). Finally, the improved effect observed by combining statins and fenofibrate may be due to a synergistic action that is independent of their cholesterol lowering effect. Despite the positive effect observed on DMO, statins were less effective in preventing the occurrence of mild DR and no recommendations could be made regarding initiating lipid lowering drugs in patients with normal serum lipid levels. Tables 3 & 4 summarise the trials that offer support or do not for the protective role of statins in DR. .

## Retinal vein occlusion

Retinal vein occlusion (RVO) is the second most common cause of retinal vascular disease after DR (83). Vision loss is secondary to macular oedema and or retinal ischaemia, which can lead to neovascularisation and high risk of tractional retinal detachment and neovascular glaucoma. Atherosclerosis, among other cardiovascular risk factors such as hyperlipdeima, diabetes and hypertension, contributes to the pathophysiology of RVO (84). Hyperlipideamia was more than twofold more common in patients with all types of RVO compared to controls (85). Raised serum lipids may change plasma viscosity and alter platelet function, which predisposes to thrombosis and blood stasis (86). A number of inflammatory cytokines and growth factors may also be upregulated in response to the onset of retinal ischaemia (87), which may predispose to a state of chronic inflammation (88). Statins, in addition to their anti-inflammatory action, were shown to have a potential protective effect on the microvascular endothelium in retinal ischaemia models (89). While low doses promoted vascular repair mechanism through upregulating VEGF and NO levels, higher doses resulted

in cell death due to depletion of intracellular cholesterol and disruption of key structures within the cell.

There is little clinical evidence regarding the role of statins in the management of RVO, or in preventing its development. A retrospective study of RVO patients, as well as patients with a high risk of developing RVO ( defined as those having hypertension and primary open angle glaucoma), no clear preventative or therapeutic benefit could be found after 43 months follow-up. (90).

## Uveitis

Uveitis mainly affects young people and carries a significant risk of vision loss (91). It can be associated with an underlying systemic disease, though most cases remain idiopathic.

Corticosteroids represent the mainstay of the treatment, however, steroids are not ideal for long-term therapy because they are associated with a wide array of side effects particularly increasing total serum cholesterol levels and induction of diabetes and hypertension, thus increasing their cardiovascular risks. Similarly, other immunosuppressive drugs may also have significant side effects including increasing cardiovascular morbidity (92).

Statins have been shown to have a number of anti-inflammatory and immunomodulatory effects, specifically their ability to reduce key inflammatory cytokines such as IL-6, IL8 and TNF  $\alpha$ , as well as prevent leukocyte adhesion to vascular endothelium (5, 22). The role of statins has been extensively studied in a mouse model of experimental autoimmune uveoretinitis, where it was found that they reduce the clinical and histological scores of

inflammation and inhibit T lymphocyte recruitment into the retina (93). In a mouse model of acute autoimmune retinal disease, statins were found to inhibit leukocyte infiltration into the retina and reduce retinal vascular leakage (94). Treatment with statins also resulted in improved vascular stability in a rodent model of lipopolysaccharides-induced liver microvascular dysfunction (95).

Clinical studies in multiple sclerosis (MS) patients showed a positive effect of simvastatin on brain atrophy suggesting these drugs cross the blood-brain barrier and can play a role in controlling inflammatory diseases. (96) In rheumatoid arthritis statins have a potential benefit in controlling disease activity manifesting as improvement in disease activity scores and reducing the number of tender and swollen joints. (97) Ocular involvement is common in many of these conditions and statins may offer an additional treatment approach to such patients. In a retrospective population-based study, use of statins was found to have a protective effect on uveitis development over a period of two years (98). The study identified 108 incident cases of uveitis with an incidence of 19% among statin users compared to 30% in patients not treated with statins. Another study also reported a twofold reduction in the risk of ocular inflammatory disease in male patients who used statins compared to a control group over a five years period (99). Although these findings did not reach statistical significance, the risk reduction was greater with longer duration of statin use. These studies suggest that statins have potential benefits in patients with ocular inflammatory disease.

To address the question of whether there could be therapeutic benefits of statins with respect to disease control and dose of anti-inflammatory medications in patients with a diagnosis of uveitis, there is an ongoing phase II RCT comparing the effect of simvastatin 80 mg once daily versus placebo among patients with sight-threatening uveitis. This may support the role of simvastatin in treating such patients, beyond reducing the cardiovascular risks related to

long-term exposure to systemic immunosuppressive drugs and corticosteroids, especially given the relatively low side effect profile of statins when compared to other immunosuppressive medications (100).

## Summary

The potential role of statins in ocular disease is supported by the understanding of their mechanism of action, not only in reducing blood cholesterol levels, but also through direct vascular and anti-inflammatory mechanisms. However, the summation of clinical studies offers conflicting results and the use of these drugs remain inconclusive. This may be related to the different treatment regimens and follow-up lengths used in the various studies, with good support for reducing the risk of CNV in AMD patients, as well as reducing the progression of DR and promoting the resolution of DMO in patients with dislipidemia. In RVO, the effect of statins was not obvious and there is limited data in other ocular diseases. As such, at this time there remains no clear recommendation to add statins, purely for their anti-inflammatory and immunomodulatory effects to the treatment of patients with ocular diseases. However, when other risk factors, such as hyperlipidaemia, diabetes and hypertension exist, statins remain an invaluable option to decrease cholesterol and reduce cardiovascular risks factors. There are encouraging results that support the role of statins in ocular diseases and further studies may provide clearer evidence in support of this treatment and offer patients additional benefits from this class of medications.

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