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Review article

Statins as anti-inflammatory agents: A potential therapeutic role in sight-threatening non-infectious uveitis

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ABSTRACT

In addition to the known lipid-lowering effects, statins are now widely accepted to have anti-inflammatory and immunomodulatory effects. Adjunctive use of statins has proven beneficial in the context of a wide range of inflammatory diseases, including rheumatoid arthritis. Evidence also suggests that statins may also have utility in the management of uveitis, a form of sight threatening inflammation which occurs in the eye. In this article, we outline our rationale behind a clinical trial of simvastatin as a steroid-sparing agent in uveitis, to which patient recruitment started last year. Potential risks associated with the clinical use of statins, including putative effects on the eyes, are discussed.

Background

Uveitis could be "the most important eye disease you've never heard of". It is a significant but largely unrecognised cause of permanent visual impairment worldwide. Uveitis denotes inflammation of the uvea, which is the highly vascular pigmented middle layer of the eye, between the sclera and the retina. The uveal tract is composed of the iris and ciliary body, anteriorly, and the choroid, posteriorly.[1] However, the term "uveitis" has now become almost synonymous in ophthalmic clinical practice with any inflammation involving structures inside the eye, including vitreous gel and the retina (Figs. 1 and 2).

In the Western world, the current incidences of uveitis vary between 38 and 200 per 100,000.[2] Many cases are chronic, and lead to numerous sight-threatening complications, including decompensation/degeneration of the cornea (the clear anterior window of the eye); cataract (opacity of the crystalline lens of the eye); raised intraocular pressure; glaucoma (optic neuropathy with a characteristic peripheral visual defect); and retinal pathology (such as macular oedema and retinal detachment), which affects retinal function (Fig. 3).

Around 10–15% of all causes of vision loss and 20% of cases legally recognised as "blindness" are attributed to uveitis.[3] It can affect people of all ages but occurs most frequently in the working age population (20–50 years), where the socio-economic impact of visual impairment is thought to be comparable to diabetic retinopathy.[4] Visual loss in uveitis has been historically underestimated due of the lack of data concerning the incidence of sight threatening complications. A recent study conducted by our group on the long-term clinical outcomes of patients attending a tertiary centre uveitis clinic indicates that the incidence of visual impairment in these patients is 19%.[5]

In the majority of cases, the aetiology of inflammation in uveitis is non-infectious and idiopathic. Non-infectious uveitis has been classically described as an autoimmune disease, mediated by Th1 and Th17 subsets of self-reactive CD4 T-lymphocytes, which secrete "signature" pro-inflammatory cytokines, specifically, interferon (IFN)-γ and interleukin (IL)-17. Our understanding of the pathogenesis of non-infectious uveitis has been facilitated by a mouse model of experimental autoimmune uveitis (EAU), in which a soluble retinal antigen and interphotoreceptor retinoid-binding protein (IRBP) are injected to create an immune response (Fig. 4).[6]

As with other forms of autoimmune inflammatory disease, the mainstay treatment of non-infectious uveitis is high dose corticosteroids with additional second-line immunosuppressive agents (such as mycophenolate, methotrexate, azathioprine or cyclosporine A), as required to reduce the corticosteroid doses and associated side effects. Corticosteroids and other immune-modulating treatments are not curative but rather suppress the immune system, thereby reducing the ocular tissue damage and detrimental consequences on vision, which result from immune system hyperactivity. The ocular side effects of corticosteroids

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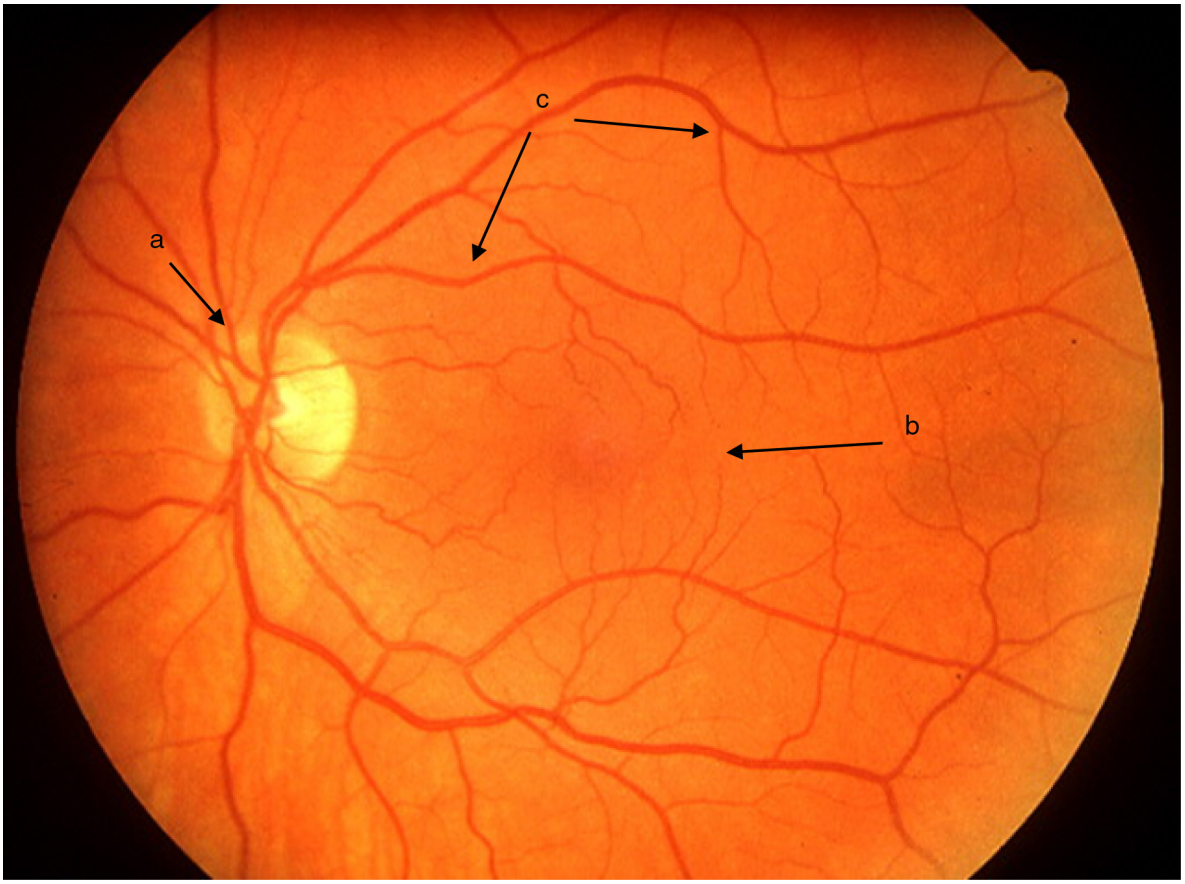

Fig. 1. Clinical retinal photography image showing the normal appearance of the retina with the following structures: (a) optic disc, (b) macular area (responsible for the central 30 degrees of vision and (c) retinal blood vessels.

include raised intraocular pressure, glaucoma and cataracts. In addition to the risk of infection associated with immunosuppression, given systemically, these drugs together have significant side effects which include hypertension, diabetes, liver dysfunction, osteoporosis and potential malignancy. In other chronic immune-related inflammatory conditions, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), it is known that there is an associated increased risk of premature atherogenesis and cardiovascular disease (CVD).[7,8] Furthermore, prescription corticosteroid use, itself, is associated with increased long-term CVD risk (Fig. 5).[9]

The burden of the current immunosuppressive drugs (costs, side effects and monitoring), plus the often relapsing and remitting course of inflammatory disease, are a major problem for patients, clinicians and ophthalmic services in the Western world. As we continue to learn more about the different mechanisms and biological pathways leading to ocular inflammation, newer biological anti-inflammatory therapeutic approaches are being developed and tested.[10] However, these therapies are expensive and the long-term safety and efficacy are not known. An alternative approach is drug re-positioning, that is, application of known drugs and compounds to treat new indications.

Statins as anti-inflammatory agents

Statins have been used for decades as a therapy for hypercholesterolemia, in order to reduce the risk of developing atherosclerosis and cardiovascular disease. They are pharmacological inhibitors of the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), into L-mevalonate, the rate-limiting step in cholesterol synthesis, by competitive blocking of the active site of the enzyme HMG-CoA reductase. Blockade of the mevalonate pathway thereby affects cholesterol production and, ultimately, reduces serum low-density lipoprotein (LDL) cholesterol levels, which are associated with increased risk of cardiovascular disease (Fig. 6).

In the cholesterol synthesis pathway, mevalonate is the precursor not only for cholesterol, but also for many non-steroidal isoprenoid compounds. The mevalonate pathway plays a vital role in various cellular functions, including cell signalling, cell differentiation and proliferation, myelination, cytoskeleton dynamics, and endocytotic/exocytotic transport.[11] There is compelling evidence that statins have pleiotropic effects, independent of cholesterol lowering, and this is due to their role in induction of post-transcriptional modifications of important isoprenoid intermediates downstream of mevalonate.[12] This process is known as "prenylation" and affects numerous signal transduction molecules in inflammatory, as well as vascular and myocardial pathways. The small guanine-triphosphate (GTP)-binding proteins, which include Rho, Rac and Ras, are an important group of proteins involved in the intracellular signalling pathways modulated by statins. These small GTP proteins regulate pro-atherogenic, pro-inflammatory pathways and are activated by isoprenylation.[13] Rho proteins, in particular, are involved in the expression of pro-inflammatory cytokines. A study proposed that simvastatin reduced the activity of RhoA, which is involved in tumour necrosis factor (TNF)-α-induction and the activation of nuclear factor (NF)-κB and cytokine secretion.[14]

Early evidence of the anti-inflammatory effects of statins derives from studies on patients with CVD. An important study that initially addressed this was the PRINCE (pravastatin inflammation/CRP evaluation) randomised controlled trial (RCT), where

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