SAVE SIGHT INSTITUTE

TOPICAL ATORVASTATIN FOR DRY EYE AND BLEPHARITIS

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THE UNIVERSITY OF SYDNEY

Save Sight Institute is a centre of The University of Sydney
No financial or proprietary interest in any material discussed

INVESTMENT HIGHLIGHTS

- Blockbuster potential drug for multibillion dollar market
- Treats the underlying causes of dry eye
- Very positive human pilot trial results
- Patented IP with well-defined regulatory pathway
- $1M required for clinical trials and improved formulation to increase value

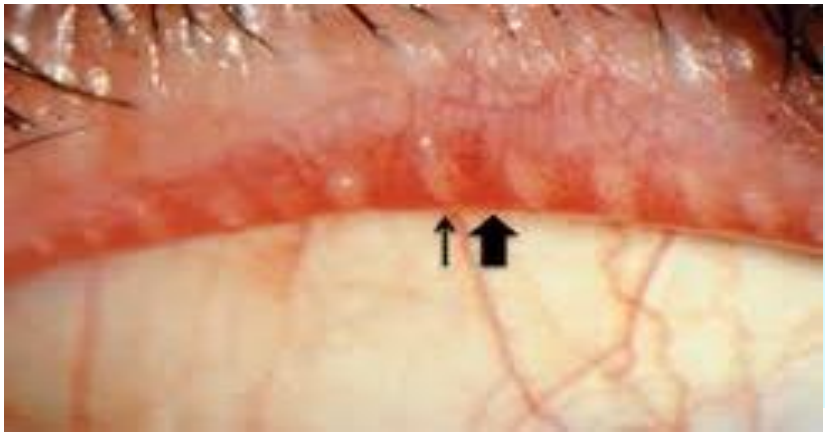
“The treatment approach is logical and initial proof-of-concept data promising” NHMRC grant assessor

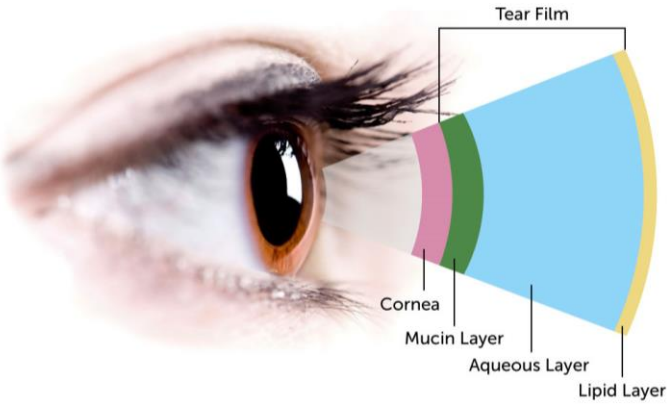
THE PROBLEM

- **1 in 5 people globally** affected by dry eye
  - Pain can be as severe as angina
  - Many continue to suffer as no solution
  - Reduced work productivity, blurred vision and ocular discomfort
  - Only a few approved treatments with limited efficacy
    - 2 drugs on market in USA (Restasis and Xiidra) but with limited efficacy, 2 in Europe, 2 in Japan
    - Artificial tears remain to be mainstay for the treatment of dry eye but they provide only temporary, symptomatic relief
    - 70% are seeking drug treatments for dry eye

DRY EYE and BLEPHARITIS

- Tears are a combination of water, mucous and oil
  - Meibomian glands in the eyelid produce the oil
  - Oil lubricates the eye and prevent tear evaporation
- Most common cause of dry eye is tear evaporation
- 80% of patients with evaporative dry eye have blepharitis





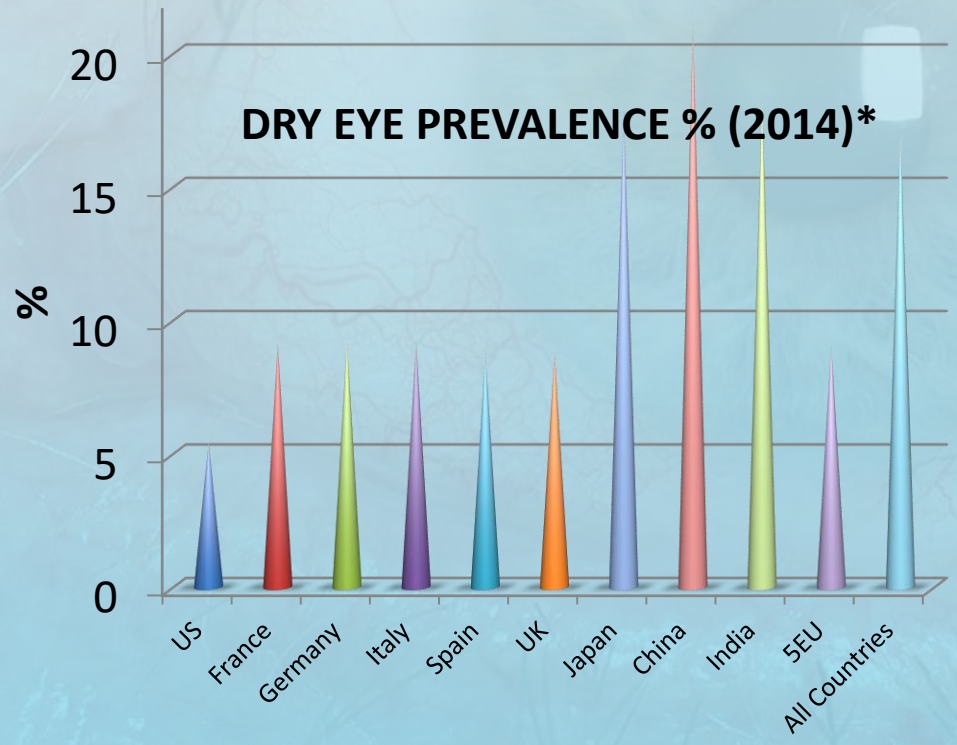
OUR TOPICAL STATIN THERAPY

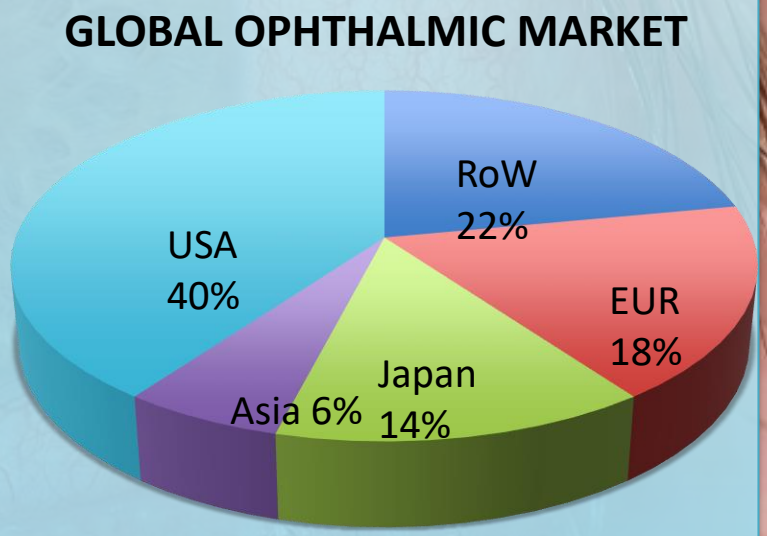
- WHAT Commonly used for hypercholesterolemia and prevention of coronary artery disease and stroke.
- WHY Selectively inhibit HMG-CoA reductase biosynthesis of triglycerides + cholesterol
  - ⬆ tear film stability
  - ⬇ inflammation
  - ⬇ bacterial lid margin load
- NOW off patent - we have repurposed atorvastatin for treatment of dry eye and blepharitis.
- IP covers evaporative dry eye (the main class of dry eye) and blepharitis.
- HOW We formulated and studied Topical Atorvastatin – toxicity, pharmacokinetics, stability, solubility

We have conducted in vitro, ex vivo and clinical pilot studies.

DRY EYE MARKET IS HUGE AND GLOBAL

- $2.7b in 2016 with a CAGR of 11.5% , ~5.5b in 2022*
- Restasis > $1 billion in USA; Diquas and Mucosta in Japan





*Global Data

CURRENT TREATMENTS

- Topical lubricants
- Anti-inflammatories (e.g. Restasis)
- Secretagogues
- Time-consuming lid massage
- No topical therapies for blepharitis

PIPELINE THERAPIES

Phase I	Mechanism	Advantage	Efficacy	Safety	Dosing	Cost
Tacrolimus 0.03%	Inactivate calcineurin	Decrease IL-2,3,4,5, IFNg and TNFa	Decreased corneal staining & OSDI scores Increased Schirmer and TBUT	Well tolera	for 84	20x > Restasis
Phase II	**Mechanism**	**Advantage**	**Efficacy**		**Dosing**	**Cost**
Anakinra = IL-1RA 2.5%	IL-1 receptor antagonist inhibits IL-1a & b to IL-1R	Decreased T cell activation , IL-1 in dry eye surface and pain	Decr	Well tolerated No IOP change	Bd for 84 days	?
Tofacitinib = JAK inhibitor	Janus kinase 1,2 &3 blocks Th1,2cytokine signalling	Decreas IL-6	creased corneal staining	Well tolerated cf Restasis	Bd for 56 days	?
Thymosin B4 = 43 amino acid peptide	Increased epitheli migration and inhibitor	eal repair ced mmation	Decreased corneal staining & OSDI Increased TBUT & vol	Well tolerated	6x/day for 28 days	?
Phase III		**Advantage**	**Efficacy**	**Safety**	**Dosing**	**Cost**
DexaSite = Dexamethasone 0.1%		Durasite extends retention	Decreased irritation	Steroid related IOP rise and cataract	Bd over 14 days	?

MOST ONLY TREAT INFLAMMATION

NEWLY TO MARKET THERAPIES

Phase III	Mechanism	Advantage	Efficacy	Safety	Dosing	Cost
Lifitegrast 5% (Xiidra)	LFA-1 inhibitor	Reduced ocular surface inflammation	Reduced inferior corneal staining score & conjunctival staining	5-25% dec. VA, dysgeusia irritation, 1-5% blurred vision, pruritus, irritation, d/c, hyperemia, h/a, sinusitis	Bd for 12 weeks	$445 for 30 days
Cyclosporine 0.1% (Ikervis)	Calcineurin inhibitor in cationic emulsion	Longer residence time, increased corneal penetration	Decreased severe keratitis in dry eye disease	Irritation, pain, lacrimation, hyperemia, eyelid erythema	Nocte for 6 months	£72 for 30 days

NEWLY TO MARKET DEVICE

COMPETITIVE ADVANTAGE

- Treats blepharitis AND dry eye
- 3 modes of action
- Well tolerated
- Human pilot data suggests more efficacy
- Established systemic safety profile
- Fast onset of action
- Potential synergy with other therapies

PILOT STUDY: VERY PROMISING RESULTS

Ophthalmic Research

Original Paper

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DOI: 10.1159/000367851

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Efficacy and Safety of Topical Atorvastatin for the Treatment of Dry Eye Associated with Blepharitis: A Pilot Study

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Key Words
Blepharitis · Dry eye · Topical atorvastatin

Abstract

Aims: To elucidate if topically applied atorvastatin safely decreases corneal fluorescein staining in dry eyes associated with blepharitis. ***Methods:*** Ten dry eye and blepharitis (DEB) patients were enroled in a prospective pilot study. All patients were treated with topical atorvastatin (50 μM) 8 times a day for 4 weeks and allowed to continue with their existing dry eye treatment. The patients were examined weekly for 4 weeks. The primary outcome measure was corneal fluorescein staining. Secondary outcome measures were tear film break-up time (BUT), Schirmer I testing, blepharitis score and bulbar conjunctival injection. The subjective efficacy was evaluated with global symptom and facial analogue scores. ***Results:*** An improvement in corneal fluorescein staining in the treated eye by >1 point from baseline to completion of the trial at week 4 was found in 9 of 10 patients ($p < 0.01$). Topical atorvastatin significantly improved the tear film BUT ($p < 0.01$), blepharitis score ($p < 0.05$) and bulbar conjunctival injection ($p < 0.05$). The global symptom score and facial analogue score also improved ($p < 0.05$). There were no side effects. ***Conclusion:*** Topical atorvastatin is a potential therapy for DEB patients. Larger comparative clinical studies are required to establish the efficacy and safety of topical atorvastatin.

Introduction

Dry eye, the most common eye disorder with up to 20% of the population affected [1–3], is frequently accompanied by blepharitis, which has an overall prevalence of nearly 40% [4, 5]. Blepharitis is more common in the ever-growing older age group [4] with close to half of the sufferers requiring treatment [6]. Patients with dry eye and blepharitis (DEB) have their daily activities disrupted [7] and work productivity lowered [8] due to recurrent blurred vision and ocular discomfort. Moderate-to-severe dry eye damages the ocular surface epithelium [9] and produces ocular surface inflammation [10].

Lipid abnormalities in meibomian gland dysfunction, including an excess of free cholesterol and cholesterol esters in tears, result in the disruption of the meibum layer with resultant evaporative dry eye and chronic DEB [11, 12]. Red, painful, irritated and itchy eyes, along with blurred vision, result from these disorders. Tear evaporation can lead to an increase in osmolarity, which produces an inflammatory response [13]. Inflammatory cell infiltration of the ocular surface epithelium, along with tear film increases in the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, IL-17, IFN-γ and TNF-α and the matrix metalloproteinase-9 occur in DEB [14–16]. Inflammatory cytokines such as IL-1, IL-6 and TNF-α can induce the keratocyte expression of matrix metalloproteinase-9 which is implicated in corneal epithelial basement mem-

PILOT STUDY: VERY PROMISING RESULTS

- Dry eye and blepharitis patients (n=10)

Analysis	Improved	No change	Worse	p value
Corneal fluorescein score	9	1	0	<0.01
Tear film BUT	10	0	0	<0.01
Blepharitis score	8	2	0	<0.05
Schirmer I test	5	0	5	>0.05
Conjunctival injection	5	5	0	<0.05

Values denote the number of patients, unless otherwise stated.

PILOT STUDY: VERY PROMISING RESULTS

Symptom	Improved	No change	Worse	p value
Global symptom score	10	0	0	0.01
Dryness	8	1	1	0.05
Foreign body sensation	10	0	0	0.01
Blurred vision	3	7	0	0.05
Discomfort	9	0	1	0.01
Photophobia	5	4	1	0.05
Redness	5	5	0	0.05
Watering	7	3	0	0.05
Face score	8	1	0	0.05

Values denote the number of patients, unless otherwise stated.

HMG CoA REDUCTASE IN HUMAN EYELIDS

Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-019-04247-9

BASIC SCIENCE

HMG-CoA reductase expression in human eyelid tissue and in a human meibomian gland epithelial cell line

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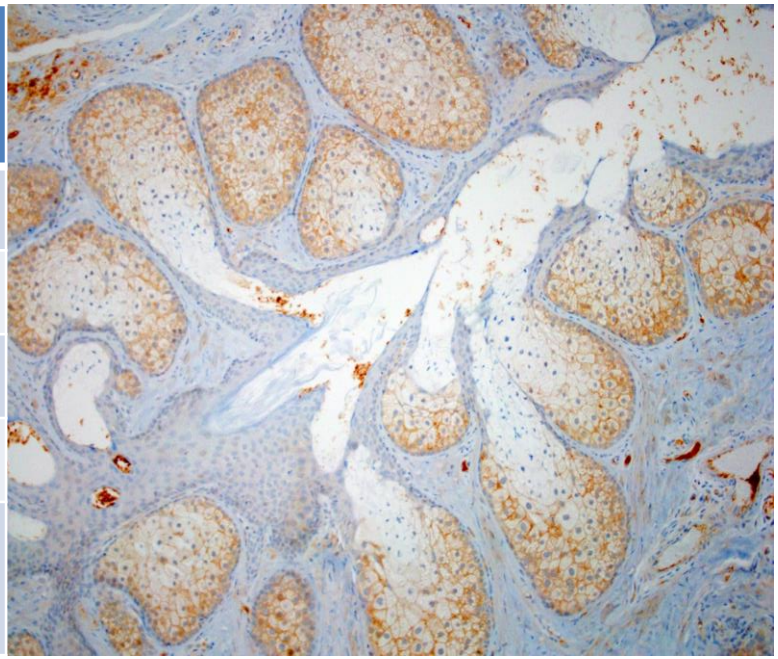
Abstract
Purpose 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), the rate-limiting enzyme of cholesterol production, has been found to contribute to lipid secretion from skin sebaceous glands and hair follicles. We assessed for HMGCR expression in human eyelid tissue and in immortalized human meibomian gland epithelial cells (HMGECs) using immunohistochemistry.
Methods Full thickness human eyelid specimens in archival paraffin blocks were obtained. A section from each block was stained with hematoxylin and eosin and examined by an ocular pathologist for validation of tissue pathology. Immunohistochemistry was performed using rabbit anti-human HMGCR antibody on serial sections using the Ventana automated staining system. HMGCR expression was examined for in HMEGCs with fluorescence immunocytochemistry and confocal microscopy.
Results Thirteen full thickness eyelid specimens met the inclusion criteria. All specimens contained meibomian glands, and 2 (15%) contained glands of Zeis, 3 (23%) pilosebaceous glands, 2 (15%), accessory lacrimal glands, and 2 (15%), glands of Moll, respectively. Immunohistochemistry showed HMGCR expression in meibocytes of meibomian glands and sebocytes of Zeis and pilosebaceous glands in all specimens. HMGCR expression was also evident in vascular endothelium. Immunofluorescence was positive for HMGCR expression on HMGEC cells. No labeling was seen for the negative Ig control.
Conclusion HMGCR was expressed in all eyelid sebaceous-type glands and in HMGECs, consistent with a role for cholesterol production in the genesis of tear film lipids. The observed expression also provides a rationale for using topical statins, inhibitors of HMGCR, as novel tear film lipid stabilizers in conditions such as blepharitis, where meibum production is aberrant.

Keywords HMG-CoA reductase · Statin · Cholesterol · Meibomian gland · Blepharitis · Dry eye · Vascular endothelium

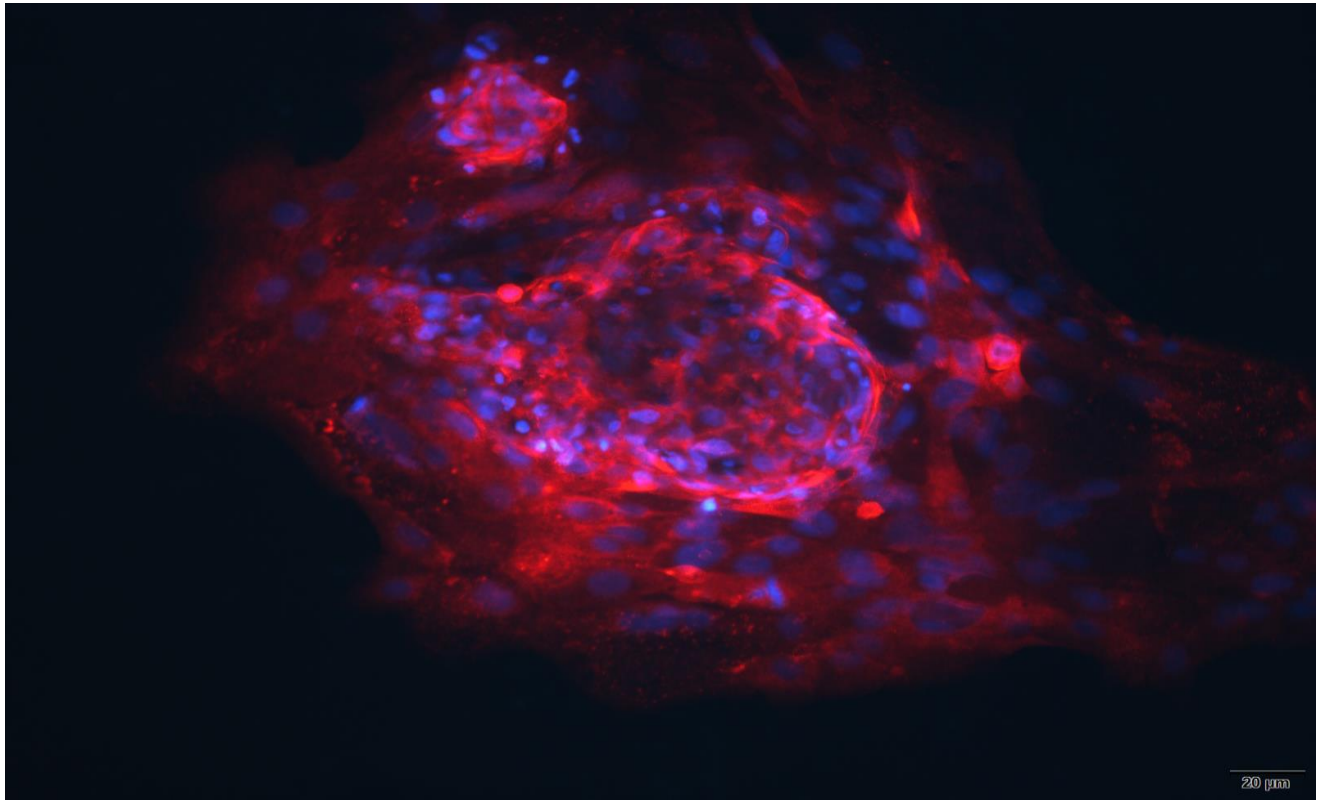
HMG CoA REDUCTASE IN HUMAN EYELIDS

- Supports mechanism of action
- Paraffin embedded archival tissue study
- Anti-human HMG-CoA Reductase Ab

Gland	n	HMG Co-A reductase receptor
Meibomian	13	13 (100%)
Zeiss	3	2 (100%)
Moll	2	0
Pilosebaceous	3	3 (100%)
Accessory lacrimal	2	0



HMG CoA REDUCTASE IN HUMAN MEIBOMIAN GLAND EPITHELIAL CELL LINES



Immunofluorescence: Meibomian gland cell nuclei in blue and HMG-CoA reductase in red

EPIDEMIOLOGICAL STUDY

Oral statins cannot be used in the treatment of dry eye

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DOI: 10.1111/ceo.13388

WILEY Clinical & Experimental Ophthalmology

ORIGINAL ARTICLE

Association of dyslipidaemia and oral statin use, and dry eye disease symptoms in the Blue Mountains Eye Study

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Importance: There is limited literature on oral statin use and its association with dry eye.
Background: To analyse the association between dyslipidaemia, use of oral statin drugs, and symptoms of dry eye disease (DED) among older adults.
Design: Population-based study.
Participants: Participants of the Blue Mountains Eye Study III (BMESIII), a large cohort study in suburban Sydney, aged 60 years or older (mean age = 74, range = 60–97, n = 1680) were analysed.
Methods: Information on DED symptoms and statin use were obtained from an interviewer-administered questionnaire. Serum lipid profiles were determined from fasting blood tests.
Main Outcome Measures: The association of various DED symptoms, as well as their number and their severity, with dyslipidaemia and oral statin intake was evaluated.
Results: At least one DED symptom was reported in 52% (n = 1029) of the population. Patients with hypercholesterolaemia (>5.5 mmol/L) did not report more DED symptoms than those without hypercholesterolaemia. Neither serum high-density lipoprotein nor low-density lipoprotein levels were associated with any DED symptoms. Patients taking oral statins were more likely to report one or more moderate to severe symptoms of DED (odds ratio: 2.054, 95% confidence interval: 1.281–3.295).
Conclusions and Relevance: The association between oral statin use and presence of moderate to severe DED symptomatology is a novel finding that deserves further mechanistic and clinical correlation in order to determine its potential, or lack thereof, for the management of dry eye.

KEYWORDS
dyslipidaemia, hypercholesterolaemia, lipid, Meibomian gland dysfunction, statin

STATIN REVIEW PAPER

https://www.eyeworld.org/getting-heart-potential-statin-use-eye

Surv Ophthalmol. 2019 May - Jun;64(3):401-432. doi: 10.1016/j.survophthal.2019.01.013. Epub 2019 Jan 28.

Statins in ophthalmology.

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Author information

Abstract

Statins, 3-hydroxy-3-methyl-gutaryl coenzyme A reductase inhibitors, are a class of lipid-lowering drugs with anti-inflammatory, immunomodulatory, and vascular effects. Statins are increasingly being used in the treatment of a variety of medical conditions. We examine the actions of statins on the eye and its associated ophthalmic disorders. Statins can be synthetic or nonsynthetic, and their differentiating derivations may contribute to their varying cholesterol-lowering and pleiotropic effects. There is conflicting evidence on the ocular therapeutic and adverse effects of the statins. Statins may play a role in reducing the burden of dry eye, corneal ulcer scarring, thyroid-associated orbitopathy, glaucoma, uveitis and other associated ocular inflammatory states, cataract, proliferative vitreoretinopathy, diabetic retinopathy, macular degeneration, and choroidal melanoma. Topical preparations of statins can be formulated, thereby extending the range of ocular diseases that may be amenable to treatment. Statins have a relatively safe side effect profile, but rare and serious adverse reactions have been reported with their usage in ophthalmology, including myopathies and rhabdomyolysis with acute renal failure.

KEYWORDS:

age-related macular degeneration; blepharitis; cataract; cornea; diabetic retinopathy; dry eye; glaucoma; retina; statins; uveitis

TEAM

Prof. Stephanie Watson

Eye Surgeon

PhD in Dry eye therapies

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MSurg (Ophth) on the immunomodulatory effects of statins in uveitis

ADVISORS

Dry eye trial development

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IP advice

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Medical advisory team

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INTELLECTUAL PROPERTY

Existing IP

- Methods of use IP: coverage for blepharitis, evaporative-intrinsic dry eye (the dominant dry eye subclass) and other ocular surface inflammatory disorders characterised by an unstable tear film
- National phase patent applications filed in US, Europe, Australia, China and Japan
  - *The above territories capture >70% of the world's ophthalmic market*
- IP status: Patent nowfully granted in Japan, Europe, Australia and awaiting clearance of amendments in US
- Detailed IP assessment performed by Freehills; strategy for responding to prior art is in place

Future IP

- Dosage IP (e.g., optimal dosage based on patients' dry eye) generated through the proposed clinical trial
- Formulation IP (e.g., strategies to increase solubility of atorvastatin; sustained release gel formulations containing statins)
- Detailed IP strategy document is in development

GUIDANCE RECEIVED

- Feedback from CROs (ORA)
  - Placebo controlled trial with recognised endpoints will increase value
- Interest from Accelerating Commercialisation, a program administered by AusIndustry
- Innovation award from UNSW
- Initial regulatory advice recommends clinical trials in Australia before developing data for the USA
- Positive patient interest and independent clinician support

RISKS AND THEIR MITIGATION

RISK	MITIGATION
Pilot efficacy does not hold for larger patient numbers	Pursue combination therapies to increase efficacy Improve formulation
Off-label generic competition	IP strategy for most common type of dry eye not covered by prior art Pursue combination therapies to increase efficacy Improved formulation development
Efficacy on blepharitis does not exceed manual lid regime standard of care	Target dry eye as main market Combination with manual regimen could increase efficacy
Safety issues	Continue to follow pilot study patients without ill effects Long history of oral statin use

EXPANDED INDICATIONS

- **Post-cataract dry eye**
- Post-refractive surgery dry eye
- Corneal Ulcer (ulcerative Keratitis)
- Allergic Conjunctivitis
- Rosacea keratitis
- Pterygium
- Ocular Inflammation
- Ocular Pain
- Post-intravitreal injection dry eye

TOPICAL ATORVASTATIN

A welcome "SIGHT FOR DRY EYES"

in a growing market

Solutions for Sore Eyes Youtube Video
http://youtu.be/pXrcdi3UoHA

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