DR KENNETH G-J OOI
MBBS, MSURG, FRANZCO
CLINICAL SENIOR LECTURER
SAVE SIGHT INSTITUTE
UNIVERSITY OF SYDNEY

TOPICAL STATINS FOR BLEPHARITIS AND DRY EYE

(EXPANDED INDICATIONS)

ALLERGIC CONJUNCTIVITIS

- Types
  - Seasonal
  - Perennial
  - Atopic keratoconjunctivitis
  - Vernal keratoconjunctivitis
  - Contact lens papillary
- 40% of the population Zeki
- 30% underdiagnosed & untreated Zeki
- Topical steroids for severe cases Zeki
- Global US$2 Bn market

Dupuis *et al.*
Allergy Asthma Clin Immunol (2020) 16:5
https://doi.org/10.1186/s13223-020-0403-9

A contemporary look at allergic conjunctivitis

Pascale Dupuis[1*], C. Lisa Prokopich[2], Alexander Hynes[3] and Harold Kim[1,4]

Abstract

Allergic eye disease is common, yet often overlooked in North America. In the U.S., up to 40% of the population is deemed to be affected and this number is growing. Symptoms and signs of ocular allergy can lead to decreased productivity and negatively impact quality of life (QoL). Various treatment options exist to achieve symptom control. For allergic conjunctivitis, ophthalmic agents include antihistamines, mast cell stabilizers, dual-activity agents, nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and some off-label treatments. Immunotherapy is recommended as a therapeutic option. This review provides a summary of the forms of ocular allergies, with a focus on symptoms and signs, impact on QoL, physical examination, diagnosis and therapeutic options of allergic conjunctivitis. Through multidisciplinary collaborations, a simplified algorithm for the treatment of allergic conjunctivitis is proposed for Canadian clinical practice.

Keywords: Allergic conjunctivitis, Allergic eye disease, Ocular allergy, Allergic conjunctivitis diagnosis, Allergic conjunctivitis treatment algorithm, Interprofessional management

https://www.prnewswire.com/news-releases/global-2-bn-allergic-conjunctivitis-market-2025---seasonal-allergic-conjunctivitis-sac--perennial-allergic-conjunctivitis-pac-hold-majority-of-market-300794158.html

ALLERGIC CONJUNCTIVITIS

- Proposition
  - Topical statins may reduce allergic conjunctivitis dry eye and inflammation mediated by Il-4, IL-5
- Evidence
  - Atorvastatin reduces IL-4, IL-5 Jameel
  - Simvastatin reduces IL-4, IL-5 Al-Sawalha
  - Elevated IL-4, IL-5 in asthma Al-Sawalha
  - Statins proposed for repurposing as inhalation agents for asthma Zeki

Hindawi Publishing Corporation
Journal of Ophthalmology
Volume 2016, Article ID 5072781, 7 pages
http://dx.doi.org/10.1155/2016/5072781

Research Article

Expression of TSLP and Downstream Molecules IL-4, IL-5, and IL-13 on the Eye Surface of Patients with Various Types of Allergic Conjunctivitis

Xiaofen Zheng, Juan Yao, and Bing Li
Department of Corneal Diseases, Shanxi Eye Hospital, Fu Dong Street No. 100, Xinghualing District, Taiyuan City, Shanxi Province, China
Correspondence should be addressed to Bing Li; libingeye@126.com
Received 12 March 2016; Accepted 17 June 2016
Academic Editor: George M. Saleh

Background. The pathogenesis of allergic conjunctivitis has not been clearly established.Moreover, previous studies fail to consider
human models of allergic conjunctivitis. This study investigated the expression of thymic stromal lymphopoiet in TSLP and its downstream molecules in conjunctival scrappings and tear. *Methods.* This cross-sectional study compares patients with vernal keratoconjunctivitis (VKC), seasonal allergic conjunctivitis (SAC), and perennial allergic conjunctivitis (PAC) with normal controls.There are 80 people recorded in Shanxi Eye Hospital. Increasingly, 20 are with VKC, 20 are with SAC, 20 are with PAC, and the remaining 20 are normal controls. Conjunctiva were harvested for total RNA extraction and gene expression by real-time
polymerase chain reaction. Epithelial cells were collected to make pathological sections for immunohistochemical staining.Human
tears were evaluated by Luminex microbead assay. A P value less than 0.05 from Dunnett's post hoc test in SPSS means a statistical
significant distinction. *Results.* Positive expression in conjunctival cells of patients with allergic conjunctivitis. The expression of TSLP and IL-4, IL-5, and IL-13 mRNA shows a statistically significant difference ($P < 0.05$). TSLP and IL-4, IL-5, and IL-13 concentrations show a statistically significant difference ($P < 0.01$). *Conclusions.* This study suggests that TSLP and downstream molecules are expressed in patients with various types of allergic conjunctivitis.

REFERENCES

- Al-Sawalha NA, Knoll BJ. Pharmacology. 2016;98(5-6):279-283. doi: 10.1159/000449062. Epub 2016 Sep 8. PMID: 27603525. Statins in Asthma: A Closer Look into the Pharmacological Mechanism of Action.
- Dupuis P, Prokopich CL, Hynes A, Kim H. Allergy Asthma Clin Immunol. 2020 Jan 21;16:5. doi: 10.1186/s13223-020-0403-9. eCollection 2020. PMID: 31993069. A contemporary look at allergic conjunctivitis.
- Jameel A, Ooi KG, Jeffs NR, Galatowicz G, Lightman SL, Calder VL. Int J Inflam. 2013;2013:434586. doi: 10.1155/2013/434586. Epub 2013 Sep 18. Statin Modulation of Human T-Cell Proliferation, IL-1β and IL-17 Production, and IFN-γ T Cell Expression: Synergy with Conventional Immunosuppressive Agents.
- Zeki AA, Elbadawi-Sidhu M. Expert Rev Respir Med. 2018 Jun;12(6):461-473. doi: 10.1080/17476348.2018.1457437. Epub 2018 May 3. PMID: 29575963. Innovations in asthma therapy: is there a role for inhaled statins?
- Zheng X, Yao J, Li B. J Ophthalmol. 2016;2016:5072781. doi: 10.1155/2016/5072781. Epub 2016 Jul 18. PMID: 27504196. Expression of TSLP and Downstream Molecules IL-4, IL-5, and IL-13 on the Eye Surface of Patients with Various Types of Allergic Conjunctivitis.

OCULAR PAIN

- Gaining recognition as public health problem given prevalence, morbidity and cost Galor
- In dry eye ocular pain some patients have chronic pain Galor
- Similar underlying mechanisms in dry eye and neuropathic pain – inflammation and neurogenic inflammation Galor
- Topical anti-inflammatories often used in treatment of chronic pain by targeting nerve sensitization pain amplification Galor

Ocul Surf. 2017 July ; 15(3): 404–437. doi:10.1016/j.jtos.2017.05.002.

TFOS DEWS II pain and sensation report

Carlos Belmonte, MD, PhDa,*, **Jason J. Nichols, OD, PhD**b, **Stephanie M. Cox, OD**b, **James A. Brock, D.Phil**c, **Carolyn G. Begley, OD, MS**d, **David A. Bereiter, PhD**e, **Darlene A. Dartt, PhD**f,g, **Anat Galor, MD, MSPH**h,i, **Pedram Hamrah, MD**j,k, **Jason J. Ivanusic, PhD**c, **Deborah S. Jacobs, MD**l, **Nancy A. McNamara, OD, PhD**m,n, **Mark I. Rosenblatt, MD, PhD**o, **Fiona Stapleton, MCOptom, PhD**p, and **James S. Wolffsohn, FCOptom, PhD**q

Abstract

Pain associated to mechanical and chemical irritation of the eye surface is mediated by trigeminal ganglia mechano- and polymodal nociceptor neurons while cold thermoreceptors detect wetness and reflexly maintain basal tear production and blinking rate. These neurons project into two regions of the trigeminal brain stem nuclear complex: ViVc, activated by changes in the moisture of the ocular surface and VcC1, mediating sensory-discriminative aspects of ocular pain and reflex blinking. ViVc ocular neurons project to brain regions that control lacrimation and spontaneous blinking and to the sensory thalamus. Secretion of the main lacrimal gland is regulated dominantly by autonomic parasympathetic nerves, reflexly activated by eye surface sensory nerves. These also evoke goblet cell secretion through unidentified efferent fibers. Neural pathways involved in the regulation of Meibonian gland secretion or mucins release have not been identified.

In dry eye disease, reduced tear secretion leads to inflammation and peripheral nerve damage. Inflammation causes sensitization of polymodal and mechano-nociceptor nerve endings and an abnormal increase in cold thermoreceptor activity, altogether evoking dryness sensations and pain. Long-term inflammation and nerve injury alter gene expression of ion channels and receptors at terminals and cell bodies of trigeminal ganglion and brainstem neurons, changing their excitability, connectivity and impulse firing. Perpetuation of molecular, structural and functional disturbances in ocular sensory pathways ultimately leads to dysestesias and neuropathic pain referred to the eye surface. Pain can be assessed with a variety of questionaires while the status of corneal nerves is evaluated with esthesiometry and with in vivo confocal microscopy.

OCULAR PAIN

- Proposition
  - Topical statins may reduce ocular pain as pro-inflammatory cytokines:IL-1β, IL-6, and TNF-α and anti-inflammatory cytokines such as IL-10 are involved in pathological pain. Zhang
  - MMP-9 reduction on nerve function Galor
- Evidence
  - Atorvastatin reduces IL-1β, IL-6 Jameel
  - Atorvastatin increases IL-10 Jameel
  - Atorvastatin reduces MMP-9 Mohebbi
  - Doxycycline reduces MMP-9 in ocular rosacea Lam-Franco
  - Preclinical studies: statin neuropathic pain reduction by inflammation reduction Bhalla

Int Anesthesiol Clin. 2007 ; 45(2): 27–37. doi:10.1097/AIA.0b013e318034194e.

Cytokines, Inflammation and Pain

Jun-Ming Zhang, MSc, MD[1] and **Jianxiong An, MSc, MD**[2]
[1]Department of Anesthesiology, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, Ohio, 45267-0531
[2]Department of Anesthesiology and Pain Medicine, Tsinghua University Yuquan Hospital, #5 ShiJingShan Road, Beijing, 100049, China

Abstract

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both proinflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons. Certain inflammatory cytokines are also involved in nerve-injury/inflammation-induced central sensitization, and are related to the development of contralateral hyperalgesia/allodynia. The discussion presented in this chapter describes several key pro-inflammatory cytokines/chemokines and anti-inflammatory cytokines, their relation with pathological pain in animals and human patients, and possible underlying mechanisms.

REFERENCES

- Neuropathic ocular pain: an important yet underevaluated feature of dry eye. Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD. Eye (Lond). 2015 Mar;29(3):301-12. doi: 10.1038/eye.2014.263. Epub 2014 Nov 7. PMID: 25376119
- Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, Dartt DA, Galor A, Hamrah P, Ivanusic JJ, Jacobs DS, McNamara NA, Rosenblatt MI, Stapleton F, Wolffsohn JS. Ocul Surf. 2017 Jul;15(3):404-437. doi: 10.1016/j.jtos.2017.05.002. Epub 2017 Jul 20. TFOS DEWS II pain and sensation report.
- Bhalla S, Singh N, Jaggi AS. J Pain. 2014 Nov;15(11):1069-1080. doi: 10.1016/j.jpain.2014.06.012. Epub 2014 Jul 30. PMID: 25086324. Statins: do they aggravate or ameliorate neuropathic pain?
- Galor A, Moein HR, Lee C, Rodriguez A, Felix ER, Sarantopoulos KD, Levitt RC. Ocul Surf. 2018 Jan;16(1):31-44. doi: 10.1016/j.jtos.2017.10.001. Epub 2017 Oct 12. PMID: 29031645. Neuropathic pain and dry eye.
- Jameel A, Ooi KG, Jeffs NR, Galatowicz G, Lightman SL, Calder VL. Int J Inflam. 2013;2013:434586. doi: 10.1155/2013/434586. Epub 2013 Sep 18. Statin Modulation of Human T-Cell Proliferation, IL-1β and IL-17 Production, and IFN-γ T Cell Expression: Synergy with Conventional Immunosuppressive Agents.
- Mohebbi N, Khoshnevisan A, Naderi S, Abdollahzade S, Salamzadeh J, Javadi M, Mojtahedzadeh M, Gholami K. Daru. 2014 Jan 7;22(1):10. doi: 10.1186/2008-2231-22-10. PMID: 24397933. Effects of atorvastatin on plasma matrix metalloproteinase-9 concentration after glial tumor resection; a randomized, double blind, placebo controlled trial.
- Zhang JM, An J. Int Anesthesiol Clin. 2007 Spring;45(2):27-37. doi: 10.1097/AIA.0b013e318034194e. PMID: 17426506 Cytokines, inflammation, and pain.
- Lam-Franco L, Perfecto-Avalos Y, Patiño-Ramírez BE, Rodríguez García A. Ophthalmic Res. 2018;60(2):109-114. doi: 10.1159/000489092. Epub 2018 Jun 6. PMID: 29874670. IL-1α and MMP-9 Tear Levels of Patients with Active Ocular Rosacea before and after Treatment with Systemic Azithromycin or Doxycycline.

CORNEAL WOUND HEALING

- Proposition
  - Topical statins may reduce corneal stromal wound healing scarring.
  - Repair is given a more regenerative character through TGF-beta inhibition. Ferguson
  - Topical statins may reduce pain of corneal epithelial defects without inhibition of wound healing.
- Evidence
  - Atorvastatin reduces TGF-beta Guimaraes
  - TGF-beta inhibition may allow modulation of fibrosis after refractive surgery Jester
  - Atorvastatin maintains proliferation and viability of corneal and conjunctival cells Ooi

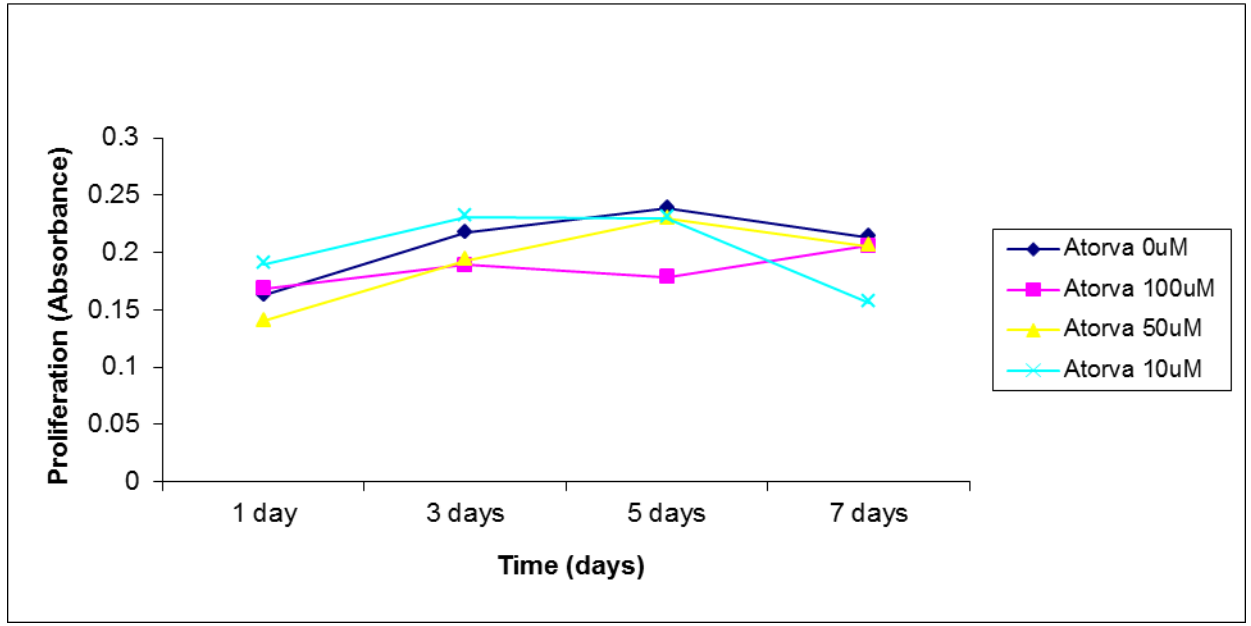

Fig. 1. Line graph showing effects of various topical Atorvastatin (Atorva) concentrations on corneal epithelial cell proliferation over 7 days using a tetrazolium MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay (ATCC, Manassas, VA 20108 USA).

REFERENCES

- Ferguson MW. J Interferon Res. 1994 Oct;14(5):303-4. doi: 10.1089/jir.1994.14.303. PMID: 7861039. Skin wound healing: transforming growth factor beta antagonists decrease scarring and improve quality.
- Guimarães DA, Rizzi E, Ceron CS, Martins-Oliveira A, Gerlach RF, Shiva S, Tanus-Santos JE. Redox Biol. 2015 Dec;6:386-395. doi: 10.1016/j.redox.2015.08.017. Epub 2015 Aug 31. PMID: 26343345. Atorvastatin and sildenafil decrease vascular TGF-β levels and MMP-2 activity and ameliorate arterial remodeling in a model of renovascular hypertension.
- Jester JV, Barry-Lane PA, Petroll WM, Olsen DR, Cavanagh HD. Cornea. 1997 Mar;16(2):177-87. PMID: 9071531 Inhibition of corneal fibrosis by topical application of blocking antibodies to TGF beta in the rabbit.
- Ooi KG, Wakefield D, Billson FA, Watson SL. Ophthalmic Res. 2015;54(1):26-33. doi: 10.1159/000367851. Epub 2015 Jun 5. PMID: 26068735. Efficacy and Safety of Topical Atorvastatin for the Treatment of Dry Eye Associated with Blepharitis: A Pilot Study.

POST-CATARACT SURGERY DRY EYE

- Impact
  - Corneal tear film is the first refractive plane and interference leads to unfavorable refractive results Alio
  - Mulitfocality requires neuroadaptation otherwise glare, confusion and distortion ensue Alio
  - Multifocal lenses and dry eye syndrome (DES) reduce contrast sensitivity Alio, Szczotka and increase dysphotopsias Alio, Woodward
  - Post-op ametropia (29%) and dry eye (15%) lead to blurred vision with multifocal IOL Woodward
  - Most frequent complaints – DES (35%) and ametropia (57%) and concurrent complaints (16%) Gibbons
  - DES and ametropia also amenable to conservative Rx with success rates of 68 – 84% Gibbons, Woodward, de Vries

POST-CATARACT SURGERY DRY EYE

- Incidence / Prevalence
  - Pre-op incidence of DES (n=136) – 63%, TBUT < 5s, 77% corneal staining, 22% previous dry eye dx Trattler
  - Post-op incidence of DES up to 30% in normal patients Miyake in Hanyuda
  - Post-op abnormal OSDI 9.8%, TBUT 68.4%, corneal staining 58.7%, Schirmer I test 11.9% at day 7 Kasetsuwan
  - Post-op TBUT significantly lower at 2 months in dissatisfied patients cf satisfied ($p<0.045$) Szakats
  - Post-op incidence of increased OSDI scores normalizes at 3 months in normal patients (n=96) Ishrat, Kasetsuwan
  - Post-op increased corneal staining normalized at 3 months in DES patient (n=96) Cetinkaya

POST-CATARACT SURGERY DRY EYE

- Incidence / Prevalence
  - Post-op decreased TBUT and MG loss with decreased MG expressibility at 3 months ($p \leq 0.05$) El Ameen
  - Post-op persistent pain at 6 months in 34% (n=119)Sajnani in 32% (n=86) and severe in 10% (n=86) Iglesias
  - Post-op 57% increased prevalence of corneal staining cf controls at 2.1 $\pm$ 3.4 years (n=172) Hanyuda

POST-CATARACT SURGERY DRY EYE

- Tear film changes after cataract surgery
  - No change in tear film meniscus height at 1 and 3 months [Han]
  - Significant decreases in IL-1beta, IL-6, MCP-1, TNF-alpha and IFN-gamma at 2 months cf day 1 [Park]
  - Significant increase in osmolarity to DES level but no difference at 1 month [Elksnis]
  - Increase in osmolarity associated with increased OSDI [Gonzalez-Mesa]
  - Significantly reduced lipid layer thickness in mild-moderate DES [Kim]
  - Reduced meibum quality [Park]
  - Reduced meibum expressibility [Han]

POST-CATARACT SURGERY DRY EYE

- Eyelid and lid margin changes after cataract surgery
  - Vascular engorgement of lid margin [Han]
  - Plugging of meibomian gland (MG) orifices [Han]
  - Displaced mucocutaneous junction [Han]
  - No MG loss [Han]
  - No significant change in meiboscore but gland dropout, shortening, distortion and proximal dilation [Park]
  - Trend toward worsening of meiboscore and reduced meibomian gland expression [Xiong]

POST-CATARACT SURGERY DRY EYE

- Topical therapy trials for dry eye post-cataract surgery
  - CMC 1% (Refresh Liquigel) qid [Yao]
  - Carbomer sodium hyaluronate trehalose 3% (Thealoz gel) bd vs Sodium hyaluronic acid 0.15% [Caretti]
  - Cyclosporine 0.05% bd [Chung]
  - Diquafosol 3% 6x/d [Lee]
  - Rebapimide 2% qid [Kato]
  - Semi-fluorinated alkane qid [Son]

REFERENCES

1. Multifocal intraocular lenses: An overview.
Alio JL, Plaza-Puche AB, Férnandez-Buenaga R, Pikkel J, Maldonado M.
Surv Ophthalmol. 2017 Sep - Oct;62(5):611-634. doi: 10.1016/j.survophthal.2017.03.005. Epub 2017 Mar 31

2. Impact of Dry Eye on Visual Acuity and Contrast Sensitivity: Dry Eye Assessment and Management Study.
Szczotka-Flynn LB, Maguire MG, Ying GS, Lin MC, Bunya VY, Dana R, Asbell PA; Dry Eye Assessment and Management (DREAM) Study Research Group.
Optom Vis Sci. 2019 Jun;96(6):387-396.

3. Dissatisfaction after multifocal intraocular lens implantation.
Woodward MA, Randleman JB, Stulting RD.
J Cataract Refract Surg. 2009 Jun;35(6):992-7

4. Causes and correction of dissatisfaction after implantation of presbyopia-correcting intraocular lenses.
Gibbons A, Ali TK, Waren DP, Donaldson KE.
Clin Ophthalmol. 2016 Oct 11;10:1965-1970

5. Dissatisfaction after implantation of multifocal intraocular lenses.
de Vries NE, Webers CA, Touwslager WR, Bauer NJ, de Brabander J, Berendschot TT, Nuijts RM.
J Cataract Refract Surg. 2011 May;37(5):859-65.

REFERENCES

6. Impact of Dry Eye on Visual Acuity and Contrast Sensitivity: Dry Eye Assessment and Management Study.
Szczotka-Flynn LB, Maguire MG, Ying GS, Lin MC, Bunya VY, Dana R, Asbell PA; Dry Eye Assessment and Management (DREAM) Study Research Group.
Optom Vis Sci. 2019 Jun;96(6):387-396.

7. The Prospective Health Assessment of Cataract Patients' Ocular Surface (PHACO) study: the effect of dry eye.
Trattler WB, Majmudar PA, Donnenfeld ED, McDonald MB, Stonecipher KG, Goldberg DF.
Clin Ophthalmol. 2017 Aug 7;11:1423-1430.

8. Discrepancies in Persistent Dry Eye Signs and Symptoms in Bilateral Pseudophakic Patients.
Hanyuda A, Ayaki M, Tsubota K, Negishi K.
J Clin Med. 2019 Feb 7;8(2). pii: E211.

9. Incidence and pattern of dry eye after cataract surgery.
Kasetsuwan N, Satitpitakul V, Changul T, Jariyakosol S.
PLoS One. 2013 Nov 12;8(11):e78657.

10. Dry Eye Symptoms, Patient-Reported Visual Functioning, and Health Anxiety Influencing Patient Satisfaction After Cataract Surgery.
Szakáts I, Sebestyén M, Tóth É, Purebl G.
Curr Eye Res. 2017 Jun;42(6):832-836.

REFERENCES

11. Incidence and pattern of dry eye after cataract surgery.
Ishrat S, Nema N, Chandravanshi SCL.
Saudi J Ophthalmol. 2019 Jan-Mar;33(1):34-40.

12. The course of dry eye after phacoemulsification surgery.
Cetinkaya S, Mestan E, Acir NO, Cetinkaya YF, Dadaci Z, Yener HI.
BMC Ophthalmol. 2015 Jun 30;15:68.

13. Influence of cataract surgery on Meibomian gland dysfunction.
El Ameen A, Majzoub S, Vandermeer G, Pisella PJ.
J Fr Ophtalmol. 2018 May;41(5):e173-e180.

14. Epidemiology of Persistent Dry Eye-Like Symptoms After Cataract Surgery.
Iglesias E, Sajnani R, Levitt RC, Sarantopoulos CD, Galor A.
Cornea. 2018 Jul;37(7):893-898.

15. Evaluation of dry eye and meibomian gland dysfunction after cataract surgery.
Han KE, Yoon SC, Ahn JM, Nam SM, Stulting RD, Kim EK, Seo KY.
Am J Ophthalmol. 2014 Jun;157(6):1144-1150.e1.

REFERENCES

16. Observation of Influence of Cataract Surgery on the Ocular Surface.
Park Y, Hwang HB, Kim HS.
PLoS One. 2016 Oct 3;11(10):e0152460.

17. Tear osmolarity after cataract surgery.
Elksnis Ē, Lāce I, Laganovska G, Erts R.
J Curr Ophthalmol. 2018 Sep 24;31(1):31-35

18. Meibomian gland dysfunction in cataract surgery: A novel evaluation using the Oculus Keratograph 5M
Xiong J, Leung KFC, Khoo P, Ooi KG, Watson SL.
RANZCO 2019

19. Efficacy of 1% carboxymethylcellulose sodium for treating dry eye after phacoemulsification: results from a multicenter, open-label, randomized, controlled study.
Yao K, Bao Y, Ye J, Lu Y, Bi H, Tang X, Zhao Y, Zhang J, Yang J.
BMC Ophthalmol. 2015 Mar 20;15:28.

20. Hydroxypropyl methylcellulose 2% for dry eye prevention during phacoemulsification in senile and diabetic patients.
Yusufu M, Liu X, Zheng T, Fan F, Xu J, Luo Y.
Int Ophthalmol. 2018 Jun;38(3):1261-1273.

REFERENCES

21. Efficacy of carbomer sodium hyaluronate trehalose vs hyaluronic acid to improve tear film instability and ocular surface discomfort after cataract surgery.
Caretti L, La Gloria Valerio A, Piermarocchi R, Badin G, Verzola G, Masarà F, Scalora T, Monterosso C.
Clin Ophthalmol. 2019 Jul 9;13:1157-1163.

22. The effect of topical cyclosporine 0.05% on dry eye after cataract surgery.
Chung YW, Oh TH, **Chung** SK.
Korean J Ophthalmol. 2013 Jun;27(3):167-71.

23. Effectiveness and Optical Quality of Topical 3.0% Diquafosol versus 0.05% Cyclosporine A in Dry Eye Patients following Cataract Surgery.
Lee JH, Song IS, Kim KL, Yoon SY.
J Ophthalmol. 2016;2016:8150757.

24. Conjunctival Goblet Cell Density Following Cataract Surgery With Diclofenac Versus Diclofenac and Rebamipide: A Randomized Trial.
Kato K, Miyake K, Kondo N, Asano S, Takeda J, Takahashi A, Takashima Y, Kondo M.
Am J Ophthalmol. 2017 Sep;181:26-36.

REFERENCES

25. Semi-fluorinated Alkane Eye Drops Reduce Signs and Symptoms of Evaporative Dry Eye Disease After Cataract Surgery.
Son HS, Yildirim TM, Khoramnia R, Poompokawat P, Knorz MC, Auffarth GU. J Refract Surg. 2020 Jul 1;36(7):474-480. doi: 10.3928/1081597X-20200519-01. PMID: 32644170

Efficacy of carbomer sodium hyaluronate trehalose vs hyaluronic acid to improve tear film instability and ocular surface discomfort after cataract surgery.
Caretti L, La Gloria Valerio A, Piermarocchi R, Badin G, Verzola G, Masarà F, Scalora T, Monterosso C.
Clin Ophthalmol. 2019 Jul 9;13:1157-1163.

POST-REFRACTIVE SURGERY DRY EYE

- DES 12-48% at 6 months post-LASIK Dohlman
- Increased MMP-9 in tears post-LASIK Dohlman
- Increased corneal sensitivity and faster visual recovery with topical cyclosporine Dohlman
- Given the high prevalence of refractive surgery and subsequent DES, efforts to develop safe and effective therapeutics are ongoing Dohlman

- Dry Eye Disease After Refractive Surgery. Dohlman TH, Lai EC, Ciralsky JB. Int Ophthalmol Clin. 2016 Spring;56(2):101-10. doi: 10.1097/IIO.0000000000000104. PMID: 26938341

Dry Eye Disease After Refractive Surgery

Thomas H. Dohlman, MD
Edward C. Lai, MD
Jessica B. Ciralsky, MD

Introduction

Laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) are the 2 most commonly performed corneal surgeries used to correct refractive errors. In the United States, an estimated 800,000 cases are completed each year.1 Since FDA approval was granted in 1995 (PRK) and 2000 (LASIK), significant advancements have been achieved, both in instrumentation and technique, rendering these procedures highly accessible, safe, and effective. LASIK and PRK are 2 of the most successful elective surgeries, with an estimated 95% patient satisfaction rate.2–4

Despite high patient satisfaction and overall success rates following LASIK and PRK, complications do occur, with dry eye disease being one of the most common. Symptoms of dry eye disease can significantly impact a patient's quality of life, and even interfere with activities of daily living.5,6 Chronic dry eye has also been associated with refractive regression.7 After an elective procedure, such as LASIK or PRK, these effects can be especially problematic.

INTERNATIONAL OPHTHALMOLOGY CLINICS
Volume 56, Number 2, 101–110

OCULAR INFLAMMATORY DISEASE

- Proposition
  - Topical statins may reduce scleritis and episcleritis mediated by IL-1 and TNF-alpha
- Evidence
  - Oral statins may be associated with a reduced risk for ocular inflammatory disease development including episcleritis and scleritis Yunker
  - Risk reduction increases with increasing use duration Yunker
  - Atorvastatin reduces IL-1 Jameel
  - Lovastatin reduces TNF-alpha Jameel

The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases

Clin Rheumatol (2017) 36:2307–2318

Claudia Fabiani[1] & Jurgen Sota[2] & Gian Marco Tosi [3] & Rossella Franceschini[3] & Bruno Frediani[2] & Mauro Galeazzi[2] & Donato Rigante[4] & Luca Cantarini [2]

Abstract: Interleukin (IL)-1 plays a key role in the pathogenesis and thereafter in the search for specific treatments of different inflammatory and degenerative eye diseases. Indeed, an overactivity of IL-1 might be an initiating factor for many immunopathologic sceneries in the eye, as proven by the efficacy of the specific IL-1 blockade in different ocular diseases. For instance, the uveitis in monogenic autoinflammatory disorders, such as Blau syndrome and cryopyrin-associated periodic syn-drome, or in complex polygenic autoinflammatory disorders, such as Behçet's disease, has been successfully treated with IL-1 blockers. Similarly, therapy with the IL-1 receptor antagonist anakinra has proven successful also in scleritis and episcleritis in the context of different rheumatic conditions. Moreover, interesting findings deriving from animal models of ocular dis-ease have set a rational basis from a therapeutic viewpoint to manage patients also with dry eye disease and a broadening number of ocular inflammatory and degenerative conditions, which start from an imbalance between IL-1 and its receptor antagonist.

Scleritis: Immunopathogenesis and molecular basis for therapy

Progress in Retinal and Eye Research 35 (2013) 44e62

Denis Wakefield a,*,1, Nick Di Girolamo a,1, Stephan Thurau b,1, Gerhild Wildner b,1, Peter McCluskey c,1
a School of Medical Sciences, UNSW Medicine, University of New South Wales, Sydney, NSW 2052, Australia b Klinikum der Universitat Munchen, Dept. of Ophthalmology, Mathildenstr. 8, 80336 Munich, Germany c Save Sight Institute, Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia

a b s t r a c t

Scleritis is a heterogeneous group of diseases characterized by inflammation of the sclera, which may be due to local or systemic infections or immune mediated diseases. Numerous studies over the last decade have led to significant progress in understanding the pathogenesis and treatment of this severe and potentially blinding disease. Immunological investigations of non-infectious scleritis and associated diseases have indicated that scleritis is an autoimmune disease and studies on the nature of the local inflammatory response have revealed the prominent role of T and B cells and cytokines, such as TNFalpha, which in turn has resulted in clinical trials showing the effectiveness of local steroid treatment, anti-TNF and anti-B cell therapy. The widespread use of imaging has led to the realization that posterior scleritis is more common than previously recognized and testing for ANCA antibodies has revealed the prominent role of immune mechanisms in a subset of patients with scleritis and associated systemic vasculitis.

REFERENCES

- Fabiani C, Sota J, Tosi GM, Franceschini R, Frediani B, Galeazzi M, Rigante D, Cantarini L. Clin Rheumatol. 2017 Oct;36(10):2307-2318. doi: 10.1007/s10067-016-3527-z. Epub 2016 Dec 28. PMID: 28032234. The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases.
- Jameel A, Ooi KG, Jeffs NR, Galatowicz G, Lightman SL, Calder VL. Int J Inflam. 2013;2013:434586. doi: 10.1155/2013/434586. Epub 2013 Sep 18. Statin Modulation of Human T-Cell Proliferation, IL-1β and IL-17 Production, and IFN-γ T Cell Expression: Synergy with Conventional Immunosuppressive Agents.
- Yunker JJ, McGwin G Jr, Read RW. J Ophthalmic Inflamm Infect. 2013 Jan 11;3(1):8. doi: 10.1186/1869-5760-3-8. PMID: 23514541. Statin use and ocular inflammatory disease risk.
- Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P. Prog Retin Eye Res. 2013 Jul;35:44-62. doi: 10.1016/j.preteyeres.2013.02.004. Epub 2013 Feb 26. PMID: 23454614. Scleritis: Immunopathogenesis and molecular basis for therapy.

POST-INTRAVITREAL INJECTION DRY EYE

- DES is a commonly experienced side effect with repeated intravitreal injections that may often be overlooked Laude
- Causes of dry eye with injections Laude
  - Pre-post injection antibiotic drops
  - Betadine
  - Injection disruption of the ocular surface
- Routine post-injection management with preservative-free lubricants as the only topical therapy Laude
- Overall, it would be very helpful for the industry to work out which type of treatment formulation is most suited for a particular type and severity of dry eye syndrome.Laude

- Laude A, Lim JW, Srinagesh V, Tong L. Clin Ophthalmol. 2017 Aug 16;11:1491-1497. doi: 10.2147/OPTH.S136500. eCollection 2017. PMID: 28860698. The effect of intravitreal injections on dry eye, and proposed management strategies.

Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

Review

submit your manuscript | www.dovepress.com

1491

Dovepress
http://dx.doi.org/10.2147/OPTH.S136500

The effect of intravitreal injections on dry eye, and proposed management strategies

Augustinus Laude1–3, Jimmy WK Lim1,2,Vishwanath Srinagesh4, Louis Tong2,5–7

1National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 2Singapore Eye Research Institute, 3Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; 4Krieger Eye Institute, Baltimore, MD, USA; 5Singapore National Eye Centre, 6Duke NUS Medical School, 7Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Abstract: Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents has become a commonly used treatment method for a number of ophthalmic conditions, including age-related macular degeneration. Although anti-VEGF therapy has shown promising results for many patients, there are several aspects of its application that have not been thoroughly investigated. One of these is the development and/or escalation of concurrent dry eye syndrome. Many patients undergoing treatment are already predisposed to dry eye disease due to their age and overall ocular health. As dry eye can have a substantial impact on quality of life, it has become increasingly apparent that the clinical signs and symptoms should be closely monitored and aggressively managed. This will allow for the optimization of patient comfort and visual potential. Here, we discuss the reasons why dry eye may develop during the course of repeated ocular anti-VEGF therapy, highlighting the key concerns about current practices and proposing possible solutions to improve the outcome for the patients.