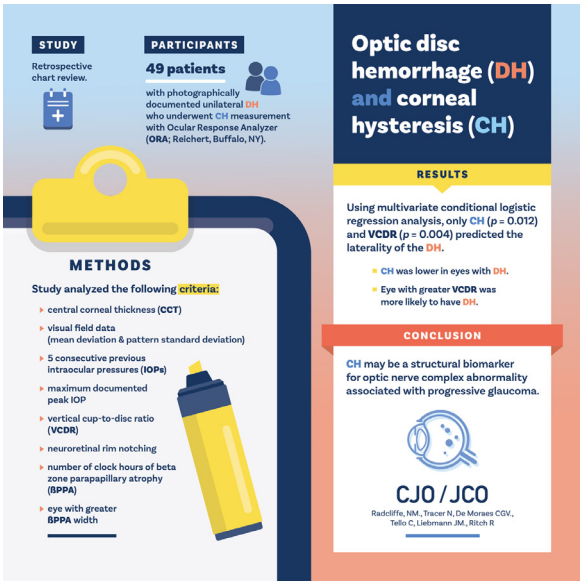

A hysteresis thesis: the importance of corneal hysteresis in glaucoma

As every ophthalmology resident learns, corneal thickness is an important piece of information to have in the glaucoma clinic. Thin corneas lead to falsely low intraocular pressure (IOP) measurements, and also predispose patients to developing glaucoma independent of this.[1] But there's another corneal parameter we should be paying attention to—hysteresis.

Corneal hysteresis is measured by the Ocular Response Analyzer, which applies a stream of air to the cornea in a crescendo-decrescendo pattern. An infrared beam detects the pressure at which the cornea first becomes flattened by the air stream before becoming concave, then measures a second pressure when the cornea returns to flat on the way to resuming its normal shape. The first pressure reading is higher than the second due to the viscoelastic properties of the cornea; the difference is the value for corneal hysteresis. Corneal hysteresis is moderately correlated with central corneal thickness in the absence of corneal pathology and it is also inversely related to IOP in a dynamic fashion.[2]

In this issue, Radcliffe and colleagues look at the relationship between optic disc hemorrhage, a known risk factor for glaucoma progression, and corneal hysteresis. Forty-nine patients from glaucoma clinic with disc photographs showing unilateral optic disc hemorrhages and lacking any corneal disease were studied. Eyes with disc hemorrhages were found to have significantly lower corneal hysteresis as well as higher IOP, higher pattern standard deviation on visual fields, and a greater vertical cup-to-disc ratio when compared to the fellow eye. Multivariate regression identified only corneal hysteresis and vertical cup-to-disc ratio as predictors of the disc hemorrhage eye.[3]

The paired design of this study controls for variables, such as age and gender, and is effective because glaucoma is an asymmetric disease. The use of disc hemorrhage presence as the dependent variable has potential difficulties, as these hemorrhages are a transient finding and may also have been present in the fellow eye at other time points not examined. Despite this, the finding of a disc hemorrhage at the single study time point was correlated to higher vertical cup-to-disc ratio in multivariate analysis as mentioned above, and the mean vertical cup-to-disc ratio, IOP and pattern standard deviation were all higher for in the disc hemorrhage eye group.

This work implicates corneal hysteresis in the progression or severity of glaucoma. Notably, a recent prospective study of glaucoma suspects found that corneal hysteresis was predictive of developing glaucoma independently of IOP and central corneal thickness. Each 1mm Hg lower corneal hysteresis resulted in a 21% increased risk of developing glaucoma.[4] Why might this be? The greater the energy absorbed or dissipated by the cornea when a force is applied, the higher the hysteresis. This may relate to the ability of the posterior sclera and lamina cribrosa to dampen spikes in IOP. In support of this, one study that induced a transient increase in IOP with a modified LASIK suction ring found that the optic cup depth increased more in eyes with low hysteresis.[5] Reversal of cupping after initiation of IOP-lowering therapy is also reduced when corneal hysteresis is lower.[6]

Progression rates of glaucoma are highly variable. It can be difficult to know quickly the patient sitting in front of you will lose vision, and how aggressively to lower IOP. Corneal hysteresis is one more tool we can add to our belts when managing patients with this potentially blinding disease.

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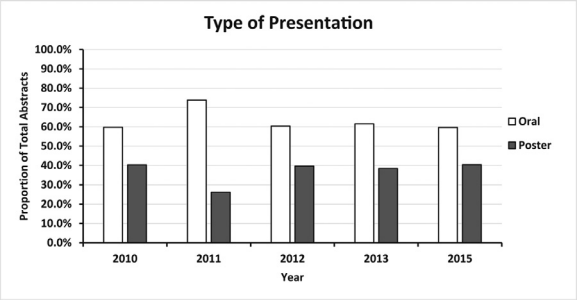

Canadian Ophthalmological Society Annual Meeting abstracts and publications: a commentary

The Canadian Ophthalmological Society (COS) hosts an annual 4-day meeting that brings together numerous ophthalmologists, residents, medical students, and other allied health professionals.[1] This educational conference is the largest of its kind in Canada for the field of ophthalmology.[1] A major component of the meeting includes the dissemination of the latest research (unpublished) and clinical updates in the form of oral presentations and posters. In general, indicators of the scientific quality of a meeting may include the likelihood of presented abstracts being published in peer-reviewed journals, the time-to-publication, and the journal impact factor or citation score.[2,3] While several studies have examined publication success for ophthalmic meetings,[3,4] very few have evaluated trends over a 5-year period. These trends and parameters become important for both attendees and event organizers for assessing meeting content and for allowing comparison to other related conferences.

In this issue, Mullen and colleagues describe the characteristics and 5-year trends in accepted abstracts from COS meetings between 2010 and 2015 (excluding 2014 as data were unavailable).[5] The authors utilized two independent reviewers to perform a database search to determine the likelihood of the successful publication of these abstracts. Including all 5 years, 42.9% of accepted meeting abstracts were published in a peer-reviewed journal with a median time-to-publication of 16 months. There were no significant differences in publication success for each of the 5 meetings included. These results are similar to the 2010 COS meeting publication success reported by Basilious et al. (45.7%)[4] and higher than a recent report from the 2012–2013 American Academy of Ophthalmology (AAO) meetings (32.7%).[3] In addition, for published abstracts, Mullen et al. reported a mean journal impact factor score of 2.39. Taken together, these indicators of the scientific quality of the COS meeting are favorable and in keeping with averages reported over a wide range of disciplines.[6]

In addition to providing metrics related to publication success, Mullen et al. highlight several interesting findings from their study. First, while there was a trend towards more publications arising from oral presentations compared to posters, this difference was not significant. Securing an oral presentation is often more competitive given the inherent time constraints. The results from this study, however, may be encouraging for prospective authors who are unsuccessful in obtaining an oral presentation as the quality of research from both poster and presentation would appear equivalent based on publication rate. Second, the authors compared the proportion of abstracts presented and those successfully published based on subspecialty type. Vision rehabilitation (9 out of 12 abstracts [75%]) and glaucoma (67 out of 129 abstracts [52%]) were the subspecialties with the highest publication rates. The authors mention that factors such as sample size and available funding may impact both the proportion of abstracts presented and those published. Nevertheless, these data can guide resource allocation and direct attention to subspecialties, such as vision rehabilitation, where additional research efforts may be needed.

In summary, Mullen and colleagues present valuable data characterizing COS abstracts and publication rates from 5 recent meetings. Endeavors such as this provide a benchmark for evaluating future meeting content and facilitate the development of strategies to further increase publication rates for accepted abstracts.

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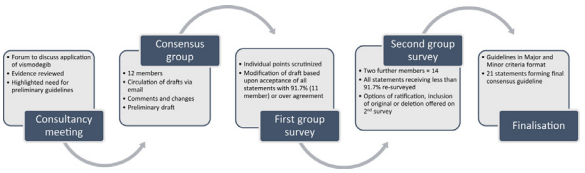

Guidelines for vismodegib in the management of periocular basal cell carcinoma: a commentary

Basal cell carcinoma (BCC) is the most frequently encountered malignancy in the periocular area, and the treatment of periocular BCC has traditionally been managed through margin-controlled excision with adjuvant radiotherapy as needed.[1] However, the treatment of metastatic and advanced BCC is challenging because it can require extensive resection with potential for recurrences. Vismodegib is an inhibitor of smoothened (SMO) in the hedgehog pathway and the first molecular-targeted oral therapy that has been approved for the treatment of BCC. Although vismodegib received Health Canada approval for use in "histologically confirmed metastatic BCC or locally advanced BCC inappropriate for surgery or radiotherapy," the appropriate use of vismodegib in clinical practice has been debated due to its cost, need for pre-approval, and side effect profile.[2]

In this issue, Hussain and colleagues report on the outcome of their study, which aimed to create a Canadian consensus framework for the use of vismodegib in BCC patients.[2] The consensus framework was developed using a modified Delphi process consisting of 12 to 14 oculoplastic surgeons in 2 rounds of online surveys. Consensus was defined to have been achieved when two-thirds of the participants were in favour of each statement. The modified Delphi process led to the development of 21 individual statements, consisting of seven preamble statements, 4 major criteria, and 11 minor criteria. The evidence for the guidelines stemmed primarily from the ERIVANCE trial that led to Health Canada's approval of vismodegib. The ERIVANCE trial demonstrated that 21% of locally advanced BCC showed complete resolution, while 43% reduced by more than 20% from the original size and 10% of metastatic BCC showed a 10% reduction from the original size.[3] However, vismodegib is not without side effects. The STEVIE trial on the safety profile of vismodegib showed that overall it was well tolerated but 98% of patients experienced one or more treatment emergent adverse events (TEAE) and 23.8% had serious TEAEs.[4] Based on the ERIVANCE trial and other recent studies, the consensus group developed the following guidelines for the use of vismodegib[2]:

- Preamble:
  - At least 1 major criterion or 2 minor criteria should be fulfilled to consider first-line treatment with vismodegib.
  - Provincial/Health Canada approval guidelines should be taken into consideration.
  - This document neither serves to support nor discourages the use of the medication.
  - Clinicians should apply these guidelines individually at their discretion.
- For all patients, ensure:
  - Multidisciplinary team review including preferably tumour board review. This should include as a minimum an oculoplastic surgeon (or a surgeon with expertise in periocular skin cancer), a radiologist, a medical oncologist, a radiation oncologist, and a pathologist. Consult head and neck surgery, neurosurgery, and plastic surgery as required.
  - A clear definition of treatment (such as control or cure) should be established with the patient and MDT/tumour board.
  - Ensure that the patient does not have any contraindications to the medication.
- Major criteria
  - Patient medically unfit to have surgery or radiotherapy.
  - Patient has metastatic BCC disease considered untreatable by surgery or radiation.
  - Surgery would lead to immediate loss of the eye.
  - Basal cell nevus syndrome with multiple facial BCCs that cannot be reasonably excised surgically.
- Minor criteria
  - BCC is located on side of only functioning eye.
  - Surgeon concern regarding functional deficit from surgery or radiation, such as:
    - BCC involving entire upper eyelid.
    - BCC involves entire lower eyelid AND medial canthus >5-mm-diameter area.

- BCC involves entire lower eyelid AND lateral canthus >10-mm-diameter area.
- BCC involving medial canthus >5-mm-diameter area and two-thirds or more of upper eyelid and/or lower eyelid.

- Sclerosing or morpheaform (infiltrative) lesion with anticipated surgical defect involving anatomy described above.
- Patient with recurrent BCC with 2 or more previous margin-controlled excisions.
- BCC involving periosteum, orbital soft tissue, or frank bone invasion clinically and/or on fine-cut neuroimaging.
- BCC with (macroscopic) perineural invasion on neuroimaging.
- Patient and surgeon both concerned that cosmetic outcome of surgery may be unacceptable.

Clinical practice point: To our knowledge, the present article is the first article to provide guidelines for the use of visemodegib in the treatment of BCC in Canada. Given that vismodegib has a significant side effect profile, the present guidelines provide evidence-based guidance on the most appropriate clinical scenarios for use of the drug.

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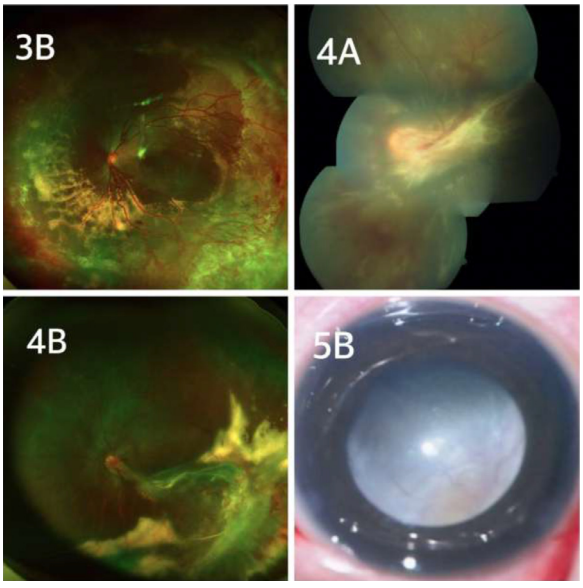

Resident perspective: outcomes of surgery in eyes with familial exudative vitreoretinopathy-associated retinal detachment

Familial exudative vitreoretinopathy (FEVR) is a rare heritable disorder of retinal angiogenesis. It has been found to arise from mutations in genes involved in the Norrin/Frizzled4 signaling pathway.[1] Mutations may arise *de novo* or be inherited in an autosomal dominant, autosomal recessive or X-linked recessive manner, with highly variable expressivity. The hallmark clinical finding is peripheral retinal avascularity. Complications result from retinal ischemia.[1] Presentation in childhood is typical but may be later depending on severity.[2] Clinical findings may be reminiscent of retinopathy of prematurity (ROP), but in the absence of a history of premature birth.

In this issue, Sen and colleagues present a retrospective surgical case series involving 44 eyes of 38 patients operated for FEVR-associated retinal detachment (RD) at a single tertiary centre in South India.[3] What is noteworthy about their series is the relatively older age at presentation compared to previous series (mean, 14.6 ± 10.9 years; range, 5 months to 51 years). This may reflect a wider range of disease severity or differences in access to care. Aspects of this article that were perhaps most relevant to residents were the spectrum and severity of disease manifestations and the surgical considerations for these types of complex RDs.

Disease manifestations. Peripheral retinal avascularity is a diagnostic criterion for FEVR. In this study, avascularity was most commonly noted for two quadrants only (57%) or for all 360 degrees (34%). In FEVR, ischemic retina may lead to retinal neovascularization and fibrosis, retinal detachment (tractional, rhegmatogenous and/or exudative), radial retinal folds, macular "dragging" (heterotopia) or, in

the most severe cases, complete retinal dysplasia.[2] Inter-ocular asymmetry may be significant. In the present series, 80% of RDs were rhegmatogenous and 20% tractional, 41% were total and 84% involved the macula. Sub-retinal exudation was observed in 21% of eyes and radial folds in 27%. Pre-operative best-corrected visual acuity was very poor (log-MAR 1.46 ± 0.7; roughly 20/600 Snellen). Fellow eyes ranged from having only peripheral avascularity (41%) to total RD (22%). Due to the spectrum of severity and profusion of possible complications, FEVR patients require life--long surveillance and examination ought to be offered to asymptomatic relatives.

Surgical considerations. In this study, detachments were treated with either scleral buckle alone (32%) or primary pars plana vitrectomy (68%). Reattachment was observed in 75% of eyes after a single surgery, and in 84% after multiple surgeries (mean, 1.23 per eye). Attachment rates were similar irrespective of the primary surgery type, suggesting that, with appropriate case selection, both are valid surgical options. Study requirements for offering primary scleral buckle were RDD due to peripheral outer retinal breaks, clear ocular media, and no significant proliferative retinopathy (PVR). Vitrectomy was preferred for eyes with posterior retinal breaks, extreme traction and PVR. Knowledge of these considerations is not only essential for trainees interested in vitreoretinal surgery but is also relevant for any ophthalmologist to be able to provide a detailed referral to a surgical retina colleague.

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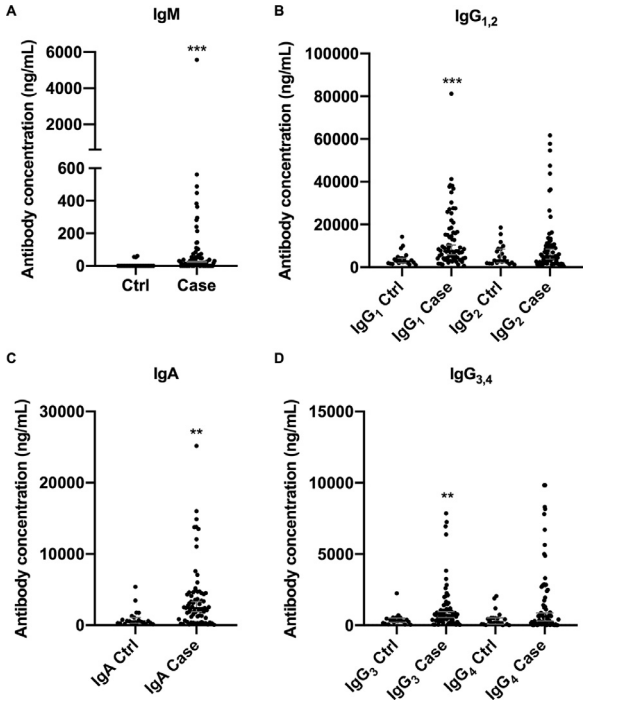

Intraocular antibodies as a novel target for understanding and treating vascular diseases of the eye

Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis and vascular permeability; its upregulation results in abnormal neovascularization and breakdown of the blood-retinal blood barrier in various ocular diseases, such as diabetic retinopathy (DR), neovascular age-related macular degeneration (nAMD), and retinal vein occlusion (RVO).[1-5] This pathophysiology forms the basis for the use of intravitreal anti-VEGF agents, representing a paradigm shift in how such ocular diseases are treated.[6-11] However, some patients prove to be poor or non-responders to anti-VEGF therapy or show a loss of efficacy over time.[12] Causes of resistance and tolerance have been suggested but the precise underlying mechanism has yet to be elucidated. Drug-induced immunogenicity has been recognized as an occasional challenge in the efficacy of biologics, leading to antidrug antibodies (ADAs) in conditions such as rheumatoid arthritis, psoriasis, and metastatic melanoma.[13-15] Perhaps a similar mechanism occurs intraocularly; in fact, circulating neutralizing antibodies against anti-VEGF ranibizumab and bevacizumab have been reported.[8,16] In this issue, Rullo et al. characterize aqueous humour antibody profiles in patients receiving anti-VEGF for retinal vascular disease compared to controls.[17]

This prospective cross-sectional study measured levels of the immunoglobulins M, G, and A (IgM, IgG, and IgA) in the aqueous humour of 71 patients receiving anti-VEGF injections for DR (22 patients), nAMD (20 patients), RVO (26 patients), and retinal artery occlusions (3 patients). They were compared to 22 control patients with no history of retinal disease or previous intravitreal injections (IVIs). Significantly higher concentrations of intraocular

immunoglobulins were measured in patients receiving IVIs. Mean IgM concentration in cases compared to controls was 150.3 ± 663.4 ng/mL and 7.7 ± 19.85 ng/mL ($p<0.0007$), respectively, and mean IgG isotype and IgA concentrations were 2- to 4-fold higher in cases versus controls. Serum antibody levels were comparable between groups. Considering the immune privilege of the eye,[18] higher intraocular antibody concentrations in disease states could be attributed to effector cell recruitment and/or efflux from inflammation-induced cell damage.[1] This explanation is consistent with antibody profiles Rullo et al. report between disease states—eyes with DR, which have more severe retinal damage compared to nAMD or RVO, have the greatest antibody concentrations. Antibodies also correlated with the number of IVIs, showing a positive correlation between number of injections and IgG_1, IgG_2, and IgG_3 levels. This could underlie the concept of drug-induced immunogenicity and treatment tolerance with continued IVIs. Furthermore, antibody titers varied according to type of anti-VEGF injected, being highest in those receiving ranibizumab, ranibizumab/aflibercept, and ranibizumab/bevacizumab combinations, and lowest in those only receiving aflibercept. This result may provide the immunological basis for switching anti-VEGF agents in nonresponders.[19-21]

Rullo et al. also explored the relationship between antibody titers and clinical parameters. Higher concentrations of IgG_1, IgG_2, and IgG_3 correlated with worse 3-month post-IVI logMAR best corrected visual acuity (BCVA), a particularly strong correlation seen in DR eyes ($r=0.622$, $p<0.001$; $r=0.719$, $p<0.001$; $r=0.724$, $p<0.001$, respectively). Persistent intra- and subretinal fluid correlated with higher IgG isotype titers, though only statistically significant with IgG_3. Thus, characterizing IgG isotype profiles translates clinically as well.

Truly treatment-naïve patients were not included in this study, and measurement of antibody levels before and after IVIs in such a group is warranted before making definitive conclusions about non-responders. However, despite certain study limitations, Rullo et al. highlight potential immunologic mechanisms of anti-VEGF resistance and tolerance. Continuing research in this area can help optimize patient outcomes and individualize treatment for poor anti-VEGF responders.

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