Canadian expert consensus: optimal treatment of neovascular age-related macular degeneration

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ABSTRACT • RÉSUMÉ

Objective: To develop a consensus concerning the management of patients with exudative age-related macular degeneration (AMD).

Methods: The development of a consensus among Canadian experts concerning optimal treatment of AMD began with a review of the clinical evidence, daily practices, existing guidelines, and current national and international approvals and policies. The experts met on June 29, 2010, in Quebec City to discuss their findings and to propose strategies for consensus.

Results: The result of this expert panel is a consensus proposal for Canadian ophthalmologists and retina specialists who are treating patients with or at risk for developing neovascular AMD.

Conclusions: The consensus provides guidelines to aid retina specialists in managing exudative AMD. Currently, ranibizumab is the only agent with sufficient Level I evidence and a Health Canada–approved indication for the treatment of wet AMD. Bevacizumab has been shown to be noninferior in preserving and improving visual acuity when compared to ranibizumab. Potential safety differences between the 2 drugs remain to be elucidated. The positioning of ranibizumab in this therapeutic area will be further defined as additional data for existing and emerging therapies become available. Until then, this agent remains the therapy of choice for individuals with neovascular AMD.

Contexte : Les nouvelles approches thérapeutiques, particulièrement les thérapies anti-facteurs de croissance endothéliale vasculaire (anti-VEGF), préviennent, et renversent en certains cas, le dommage oculaire causé par la dégénérescence maculaire liée à l’âge (DMLA). L’accès inégal aux soins à travers le Canada demeure un problème pour beaucoup de spécialistes de la rétine et leurs patients.

Objet : Développer un consensus sur la gestion des patients ayant une DMLA exsudative.

Méthodes : Document consensuel.

Participants : Dix spécialistes canadiens de la rétine.

Méthodes : Le développement d’un consensus d’experts canadiens pour le traitement optimal a commencé par une revue des données probantes cliniques, de la pratique quotidienne, des lignes directrices existantes, ainsi que des approbations et politiques courantes aux échelles nationale et internationale. Les experts se sont rencontrés à Québec le 29 juin 2010 pour discuter des données et proposer des stratégies de consensus.

Résultats : Ce panel d’experts a eu pour résultat la proposition d’un consensus pour les ophtalmologistes et les spécialistes de la rétine canadiens sur le traitement des patients atteints, ou à risque de développement, de DMLA nécrovasculaire.

Conclusions : Le consensus présente des lignes directrices pour aider les spécialistes de la rétine dans la gestion de la DMLA exsudative. Actuellement, le ranibizumab est le seul agent qui, ayant suffisamment de données probantes de Niveau 1, est approuvé par Santé Canada pour le traitement de la DMLA exsudative. S’il a été démontré que le bévacizumab n’était pas inférieur pour préserver et améliorer l’acuité visuelle comparativement au ranibizumab, il reste à éclaircir les possibilités de différence de sécurité entre les deux médicaments. La position du ranibizumab dans le secteur thérapeutique sera précisée à mesure qu’on disposera d’autres données sur les thérapies existantes et émergentes. Entre temps, cet agent demeure la thérapie de choix pour les personnes atteintes de DMLA nécrovasculaire.

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in North America.1–3 Although various risk factors have been identified, the natural history of AMD remains poorly understood.3 Currently, there is no cure for the disease; however, intravitreal antivascular endothelial growth factor (anti-VEGF) agents have significantly improved visual outcomes in patients with wet AMD. These new therapeutic approaches prevent, and in some cases reverse, vision damage caused by AMD. These new therapeutic approaches prevent, and in some cases reverse, vision damage caused by AMD. Unequal access to care across Canada remains a problem for many retina specialists and their patients.

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Given the recent developments and ongoing challenges in this therapeutic area, several Canadian retina specialists perceived a need for concise guidelines to assist ophthalmologists in treating neovascular AMD, and they formed an expert panel. Each panel member performed a systematic literature review of a specific AMD management-related topic and presented the findings during a meeting in Quebec City in June 2010. The objectives of the meeting were:

- To discuss current challenges facing management of wet AMD in Canada.
- To examine current evidence in support of anti-VEGF therapies for AMD.
- To develop a national consensus document that could serve as a practical guide to assist ophthalmologists in preventing the progression of AMD in at-risk patients.

Participants agreed on all aspects through consensus. Table 1 lists the categories used to rank the quality of evidence in support of each consensus statement.

### Epidemiology of wet AMD

According to several population-based studies,4-6 the prevalence of late AMD in developed countries ranges between 1.2% and 1.7%.4-7 In Canada, nearly 1 million individuals currently have early AMD, and approximately 250,000 have advanced forms of the disease.7 Given the aging population, the number of persons over the age of 85 years and, subsequently, those affected by AMD is expected to double over the next 25 years.

#### Risk factors

The precise mechanisms responsible for the development of AMD are not fully understood. To date, age7 and family history8 are the only nonmodifiable risk factors consistently associated with AMD. The modifiable risk factors include obesity,9,10 and smoking.11,12 Dietary intake of antioxidants, docosahexaenoic acid, and omega-3 fatty acids decrease the risk.13-15 According to the Age-Related Eye Disease Study (AREDS) Report No 8, the odds of developing advanced AMD were significantly reduced in patients receiving daily antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) plus zinc (80 mg), compared to placebo (odds ratio [OR], 0.72; 99% CI 0.52-0.98).16 Thus, the authors suggested that at-risk patients should consider taking these supplements.

Other possible risk factors for AMD are identified as female sex, light-colored irises, cardiovascular disease, and increased sunlight exposure.17 Recent evidence has revealed that environmental-stress gene interactions and pathways involved in structural changes, lipid metabolism, and inflammation play causative roles in the pathogenesis of AMD.18-23 Photo-oxidative stress also plays a role in the development of AMD.24 Photoreceptor damage, caused by photo-oxidation or by free-radical–induced lipid peroxidation, leads to abnormalities in the retinal pigment epithelium (RPE) and Bruch’s membrane.25,26

### Consensus

The consensus of the experts included the following conclusions:

1. The incidence and burden of AMD are predicted to increase dramatically over the next 25 years, with the aging of the Canadian population (Level III).
2. AMD is a multifactorial disease involving genetics, diet, lifestyle, and environment (Level III).
3. Currently, phenotype-genotype correlations are poorly understood and should be extensively examined in future studies (Level III).
4. Efforts are required to address the modifiable risk factors clearly associated with the development of AMD, particularly smoking, obesity, and nutrition (Level III).
5. Vitamin and mineral supplements should be recommended to patients at high risk for AMD progression, as per AREDS reports. Physicians should, however, be cautioned against the use of beta-carotene in smokers (Level I).

#### Pharmacology and pharmacokinetics of anti-VEGF agents

Therapeutic agents targeting VEGF inhibit the functional pathway by binding to either VEGF or its receptors. Pegaptanib (Macugen) is an aptamer, a short RNA oligonucleotide that assumes a specific 3-dimensional shape and binds with high specificity and affinity to the major soluble human VEGF isoform, VEGF165.27 Pegaptanib is well tolerated in humans and has a mean half-life of 10 days.

Currently, 2 monoclonal antibody–derived therapies are used in the treatment of wet AMD: bevacizumab (Avastin) and ranibizumab (Lucentis). Only ranibizumab is approved for this indication by Health Canada. Bevacizumab is a full-length recombinant humanized monoclonal antibody.28 In contrast, ranibizumab is a much smaller fragment derived from the same parent murine antibody as bevacizumab.29 Ranibizumab binds and inhibits multiple isoforms of biologically active VEGF in vitro and in vivo,30 but bevacizumab has different interactions with these isoforms.31

In rabbits, the vitreous half-life of 0.5 mg intravitreal ranibizumab was shorter than that of vitreous bevacizumab.
Furthermore, small amounts of intravitreal bevacizumab, but not ranibizumab, were detected in serum and in the fellow uninjected eye. In human nonvitrectomized eyes, the concentration of 1.5 mg intravitreally administered bevacizumab peaked in the aqueous humour on the first day after injection, with a half-life of 9.82 days. In vitrectomized human eyes, the half-life of intravitreal bevacizumab (1.25 mg) was 6.7 days, and the peak concentration was observed on the second day after bevacizumab injection.

Radioactivity assays have indicated that both ranibizumab and bevacizumab penetrate all retinal layers, including the RPE. Activity was also present in serum from days 1 to 7, following intravitreal injection with radioactive bevacizumab.

Consensus
The experts agreed that available pharmacokinetic data support current dosing intervals for anti-VEGF agents and that they should be applied in daily clinical practice (Level IIb).

Efficacy of VEGF inhibitors in wet AMD: comparative evidence from clinical trials
Currently, 6 well-designed, multicentre, randomized, double-blind, Phase III clinical trials provide Level I evidence in support of ranibizumab. The small (n = 40), open-label trial PrONTO provides Level III evidence. MARINA and ANCHOR evaluated the efficacy and safety of monthly ranibizumab (0.3 mg or 0.5 mg) versus sham injection (MARINA) and versus photodynamic therapy with verteporfin (V-PDT; ANCHOR). In both trials, patients treated with ranibizumab had significant improvements in visual acuity (VA) at 12 and 24 months (Fig. 1). Notably, both trials confirmed that ranibizumab should be initiated with 3 consecutive monthly injections (loading dose). Improvements during this loading phase occurred rapidly, and the largest gain in VA occurred after the first injection (Fig. 2).

PIER (n = 184) and EXCITE (n = 353) assessed the possibility of quarterly ranibizumab administration. Post hoc analysis of the PIER trial indicated that in ~60% of patients, quarterly injections were insufficient to maintain the initial VA gain, but the other ~40% maintained the initial VA benefit throughout the study. This suggests that for some patients individualized treatment regimens may be appropriate. Furthermore, SAILOR, SUSTAIN, and PrONTO suggest that although as-needed (PRN) dosing may result in some loss of initial VA gain, retreatment based on mandatory monthly assessments may optimize outcomes.

Combination therapies for wet AMD Several trials evaluated combination therapies, including a steroid, V-PDT, and ranibizumab for wet AMD. No additional safety concerns were noted in these trials, although the VA gain achieved through combination therapy was never superior to that of ranibizumab monotherapy. The EVER-
EST trial exhibited a significant difference in treatment frequency and outcome with combination therapy compared to monotherapy with either ranibizumab or PDT in patients with idiopathic polypoidal choroidal vasculopathy. Thus, combination therapy is currently reserved in some clinics for patients not responding to monotherapy with ranibizumab and in some clinics for idiopathic polypoidal choroidal vasculopathy in which sub-RPE polyps are identified on indocyanine green (ICG) angiography.

Intravitreal bevacizumab for the treatment of wet AMD Numerous small-scale studies, involving various dosing and administration schedules, suggest that intravitreal bevacizumab may be an effective therapeutic option for wet AMD, the best evidence in support of this agent being Level IIb. Therefore, the results of the Comparison of AMD Treatment Trials (CATT), the first head-to-head comparison of ranibizumab versus bevacizumab, were highly anticipated. This noninferiority (99.2% CI) trial involving 1208 patients experiencing AMD demonstrated equivalent 1-year VA outcomes (primary endpoint) with monthly bevacizumab or ranibizumab (Fig. 4). However, 1-year results with PRN bevacizumab are inconclusive. PRN ranibizumab with monthly optical coherence tomography (OCT) appears to be as effective as monthly treatments. The OCT outcomes further suggest differences in favour of ranibizumab. At 1 year these differences were not reflected in VA outcomes, so there is need for long-term data to interpret the clinical significance of the findings of the CATT.

The role of fluorescein angiography (FA) and OCT in AMD assessment The role of fluorescein angiography (FA) and OCT in AMD assessment has been addressed. Although recent studies have emphasized the importance of OCT in assessing and following patients with AMD, FA remains an important part of AMD management. It is essential for calculating lesion size when performing PDT and it reveals geographic atrophy and early choroidal neovascularization (CNV) that might be missed on OCT. Furthermore, although OCT might be very sensitive, it is not specific. Thus, in some cases, FA may be needed to define the underlying cause or to rule out an associated condition.

Consensus The consensus of the group was that:

1. Level I evidence supports the use of the ranibizumab monotherapy for CNV in AMD (Level I).
2. The CATT trial demonstrated that up to 1 year of monthly bevacizumab administration is noninferior to ranibizumab (Level I).
3. It is recommended that all eligible patients treated with ranibizumab receive an initial loading phase of at least 3 consecutive monthly injections (Level I).
4. Current clinical evidence suggests that superior VA outcomes in the maintenance phase are achieved by monthly dosing. However, when monthly dosing is not feasible, an individualized ranibizumab regimen with close monthly monitoring by OCT is an option (Level I).
5. Treatment should be maintained in the presence of disease activity unless the physician believes that there is sufficient permanent structural damage that continued treatment would provide no visual benefit (Level III).
6. FA is recommended for the diagnosis and assessment of disease activity before the initiation of therapy. OCT should be performed at baseline and is recommended as part of regular follow-up and retreatment decisions (Level IIb).
7. Evidence for combination therapy is currently lacking; nonetheless, decisionmakers should not arbitrarily restrict the use of combination therapies, including but not limited to PDT. There are no known drug-drug interactions to contraindicate consideration of combination therapy with verteporfin and anti-VEGF agents. Furthermore, combination therapies may prove to be more cost-effective and should be explored before withdrawing formulary support (Level III).
Safety of anti-VEGF agents in the treatment of AMD

Recent clinical trials have repeatedly demonstrated that intravitreal anti-VEGF agents are generally a safe treatment option for neovascular AMD for as long as 2 to 3 years.55 At present, there is sufficient evidence to support this conclusion about ranibizumab and pegaptanib, but not about bevacizumab.

A review of the safety data in evidence trials of ranibizumab, which involved 3252 patients and more than 28500 injections, revealed a high benefit-risk ratio in treating wet AMD.56 Adverse ocular events in these trials were rare, with a per-injection rate of 0.05% for presumed endophthalmitis and 0.03% for serious intraocular inflammation.56 Systemic arterial thrombotic events at 24 months were slightly increased in patients treated with ranibizumab (4.6%-5%) compared with those receiving sham (3.8%) or PDT (4.2%). In the Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) trial, the incidence of stroke was higher in patients with pre-existing risk factors, such as previous stroke or arrhythmia.57

According to a literature review of 22 clinical studies involving 12 699 bevacizumab-treated patients, increased blood pressure (0.46% of patients); cerebrovascular accidents (0.21%); and myocardial infarction (0.19%) were the most common bevacizumab-related systemic side effects.58 Nevertheless, the number of patients included in individual bevacizumab studies is too small to draw firm conclusions regarding its safety in the treatment of wet AMD, especially relative to ranibizumab. Furthermore, the CATT trial was insufficiently powered to identify differences in drug-related adverse events.59 Thus, additional analyses, longer follow-ups, and integration with other studies are necessary to establish whether higher rates of adverse systemic events (gastrointestinal and organ systems in particular) are consequences of bevacizumab therapy.

It should be noted that the CATT Investigational Drug Service supplied bevacizumab packaged in single-dose glass vials.60 Currently, in Canada, compounding pharmacies may provide both ranibizumab and bevacizumab in preloaded plastic syringes. This practice carries a risk for contamination, protein clumping, and degradation of medication over time.60

Clusters of cases of severe intraocular inflammation following intravitreal administration of bevacizumab have also been reported.61-64 Some of them had very poor visual outcomes.64

In a recent retrospective cohort study in the United States that included almost 147 000 Medicare beneficiaries with claims for AMD, ranibizumab treatment was associated with a significantly lower risk for mortality compared to PDT (hazard ratio [HR] 0.85; [95% CI, 0.75-0.95]) or to pegaptanib (HR 0.84; [95% CI, 0.74-0.95); for myocardial infarction compared to PDT (HR 0.73; [95% CI, 0.58-0.92); as well as for stroke compared to PDT (HR 0.83; [95% CI, 0.69-0.99); and to bevacizumab (HR 0.81; [95% CI, 0.68-0.98).65 Furthermore, in a secondary analysis that included only patients who received either bevacizumab (n = 21 815) or ranibizumab (n = 19 026) as first-line therapy, the adjusted HRs of mortality [0.86 [95% CI 0.75-0.98] and stroke (0.78 [95% CI 0.64-0.96) were significantly lower with ranibizumab than with bev- acizumab. The patients’ socioeconomic status, however, might be a confounding factor.66 Thus, the authors concluded that there is no statistically significant relationship between treatment groups and bleeding events or stroke.65

Gower et al. found an 11% higher risk for overall mortality (HR: 1.11; [95% CI: 1.01-1.23) and a 57% higher risk for hemorrhagic cerebrovascular accident (HR: 1.57; [95% CI: 1.04-2.37) in Medicare beneficiaries (n = 77886; 46% ranibizumab) treated with bevacizumab rather than ranibizumab.67 Although the likelihood of newly diagnosed ocular hypertension/glaucoma was 19% lower in patients given bevacizumab (HR 0.81; [95% CI: 0.71-0.93), individuals treated with bevacizumab were 80% (HR: 1.8; [95% CI: 1.2-2.8) and 11% (HR: 1.11; [95% CI: 1.01-1.23) more likely to have ocular inflammation and cataract surgery, respectively.

Consensus

The consensus of the group was that:

1. Safety data drawn from randomized clinical trials, large cohort studies, and smaller case-controlled studies are in favour of ranibizumab compared to bevacizumab (Level III).
2. Accurate diagnosis by an appropriately trained ophthalmologist is necessary to initiate and continue anti-VEGF therapy (Level III).
3. Considering the increased risk for arterial thrombotic event with anti-VEGF treatment, especially in patients with a previous history of such events, a fully informed discussion with the patient about systemic risk factors is required before beginning treatment (Level III).
4. The panel strongly recommends that ophthalmologists who perform intravitreal injections comply with proper aseptic techniques (Level III).
5. The panel encourages the development of safety databases for all anti-VEGF therapies (Level III).

Economic assessment of AMD therapies

Neovascular AMD presents a significant socioeconomic burden.68 In Canada, the annual cost per patient with wet AMD is $11 334, more than 8 times the costs for elderly persons without the condition.68

Hodge et al.69 examined the economic implications for the Canadian health care system of pharmacotherapies for neovascular AMD using a cost-effectiveness threshold of a willingness to pay $50 000 per quality-adjusted life-year (QALY). However, as the upper limit for cost-effectiveness is considered by some to be as high as $100 000 per QALY, it has been proposed that $100 000 per QALY gained should represent a cost-effective intervention and...
that $50,000 per QALY gained should represent a highly cost-effective intervention.\textsuperscript{72,73}

For all lesion subtypes, the superior efficacy of ranibizumab results in a gain in lifetime QALYs of 0.73 at a cost of $41,163, resulting in an incremental cost-effectiveness of $56,194 per QALY.\textsuperscript{69}

Consensus

Additional consensus statements included the following:

1. The panel acknowledges that the treatment with ranibizumab is on the edge of the threshold of $50,000 per QALY but is well below the threshold of $100,000 per QALY (Level IIb).
2. Ophthalmology-related QALYs are more important to patients than to policy-makers and, as such, should be taken into consideration. Cost-utility analyses in vision care should be given strong support by policy-makers (Level III).

Treating wet AMD in Canada: unmet needs, treatment gaps, and drug coverage

Treatment of wet AMD in Canada must face unmet needs, treatment gaps, and drug coverage. In Canada today, there are several unmet needs facing retina specialists, patients with AMD, and those patients’ caregivers. Access to initial diagnosis and treatment is the first issue; this problem is caused partly by the lack of trained ophthalmologists and retina specialists, as well as by busy ophthalmology practices. There is also a lack of public awareness about AMD and its consequences. The progressive downward trend in the ophthalmologist-to-population ratio (Fig. 5)\textsuperscript{74} raises a question about whether the number of trained ophthalmology specialists will be able to fulfill the demands of an aging population.

Access to wet AMD treatment across Canada Table 2 indicates coverage by provinces of treatments for wet AMD in Canada.\textsuperscript{75} The approval of reimbursement for ranibizumab has diminished the use of off-label bevacizumab for wet AMD. However, some insurance plans require that the patient pay a certain percentage of the drug costs, administration-related fees, or both. In some instances, this copayment scheme might be significant enough to deter a clinician from initiating a drug that is on the provincial formulary.

The wet AMD treatment program in British Columbia significantly differs from the reimbursement plans offered by other Canadian provinces.\textsuperscript{76} This program was introduced in June 2009 to provide global provincial funding for treatment with V-PDT, bevacizumab, or ranibizumab at the discretion of the retina specialist.

Consensus

The consensus of the group was that:

1. Key issues facing the management of wet AMD in Canada include access to initial diagnosis and treatment as well as the declining trend in the ophthalmologist-to-population ratio (Level III).
2. The expert panel recognizes the need for a comprehensive evidence-based approach to guarantee access to approved Level I-evidence drugs across Canada. Because Level I-evidence drugs should be available in a timely and uniform manner, the panel recommends a coherent plan of adoption of new therapies by formularies in each and every province (Level III).
3. The expert panel supports optimal access to medical care for all Canadians and agrees that there should be no difference in access to treatment between hosp-

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**Table 2—Coverage of treatment of wet age-related macular degeneration by province**

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Visudyne (Verteporfin)</th>
<th>Macugen (Pegaptanib)</th>
<th>Lucentis (Ranibizumab)</th>
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<tr>
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Adapted and updated from Cruess A, et al. Can J Ophthalmol. 2009;44:548-56. CDR, common drug review; DNL, do not list; LWC, list with criteria; NL, not listed NOC, notice of compliance; NR, not reviewed.

*Introduced in June 2009
Emerging therapies in the treatment of neovascular AMD

Currently, several promising drugs are candidates for the prevention and treatment of AMD in various stages of clinical development.77,78 They include novel anti-VEGF therapies, antiangiogenic agents, receptor inhibitors, and tyrosine kinase inhibitors. The VEGF trap is a modified soluble VEGF receptor analogue that binds all VEGF isoforms more tightly than do other available VEGF binding agents.79 The agent has also demonstrated promising results in clinical trials.80,81

Consensus

The panel encourages active participation in clinical trials and supports clinical research into new therapies (Level III).

Conclusion

The intravitreal anti-VEGF therapies dramatically improved outcomes for patients with wet AMD. Although the latest evidence suggests similar 1-year efficacy of both bevacizumab and ranibizumab, the bevacizumab safety data remain inconclusive. The positioning of ranibizumab in this therapeutic area will be further defined as additional data for existing and emerging therapies become available. Until then, this agent remains the therapy of choice for individuals with neovascular AMD.

Disclosure: A.C. holds no equity position with any pharmaceutical company. He has received consulting fees for advisory board meetings and honoraria for speaking engagements from a number of entities, including Alcon, Novartis, and Pfizer. A.B. has received honoraria from Novartis Ophthalmics Canada, Alcon Canada, Bayer Canada, and Bausch & Lomb. He is the National Principal Investigator for the RESPOND clinical trial on diabetic macular edema, which is sponsored by Novartis Ophthalmics. St. Michael's Hospital receives unrestricted educational grants from Novartis Ophthalmics Canada and Alcon Canada. K.C. has received consultant funding from Bayer and Novartis and research funding and speaker fees from Novartis. M.G. is a consultant for Alcon, Novartis (ACUITY program) and Bausch & Lomb. P.H. has no conflict of interest to disclose in relation to the content of this document. P.K. has received research funding from Novartis, Bayer/Regeneron, and GlaxoSmithKline. He is a consultant for Bausch & Lomb and Arctic Dx and has received honoraria from Alcon, Allergan, Novartis, and Bayer. T.S. has been a paid advisory panel member for Novartis, QLT, and Pfizer. He has also received research funding from Novartis, QLT, and Pfizer and is co-Principal Investigator for the RESPOND trial in diabetic macular edema. E.T. is a paid consultant for Alcon, Novartis, Allergan, and Bausch & Lomb. He has received speaker honoraria from Alcon, Novartis, Allergan, Bausch & Lomb, and Pfizer as well as honoraria to conduct clinical research for Novartis. G.W. has been a consultant or advisory board participant and has been involved in clinical trials for Pfizer, Novartis, Regeneron, Allergan, MD Collaborate, Arctic Dx, and Bausch & Lomb. D.W. is a consultant for Novartis, Labtician, Diagnos, Bayer, MD Collaborate, Alcon, Arctic DX, and Allergan. He has received research funding from Novartis, QLT, and Alcon.

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Although intended to provide ophthalmologists with a practical guide for management of exudative AMD, these recommendations should not be interpreted as legal standards. Furthermore, these recommendations are not to replace the clinical judgements of trained retina specialists acting according to their patients’ needs and the unique clinical circumstances. The recommendations are based on the highest level of evidence available at the time of the panel’s last review.

References


