FEATURED ARTICLE

Global Estimates of Diabetic Retinopathy Prevalence and Progression in Pregnant Individuals With Preexisting Diabetes: A Meta-analysis

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We have recently published a systematic review and meta-analysis of the prevalence and progression of diabetic retinopathy (DR) in pregnant populations with preexisting diabetes. In a recent letter by Zhou and Shen, it was suggested that linear random-effects models have a limitation in analyzing pooled estimates from studies with small to moderate sample sizes, such as those in our recent meta-analysis. We chose to use the Freeman-Tukey double-arcsine transformation (FTT) method for our random-effects model for reasons previously discussed. However, generalized linear mixed modeling (GLMM) is a relatively newer method that can avoid the mentioned issues. Therefore, as an exercise, we have repeated our meta-analyses using GLMM methods and present the outcomes from both the (published) FTT and GLMM methods with the inclusion of prediction intervals, as suggested by Zhou and Shen.

Overall estimates of prevalence and progression from FTT and GLMM methods are extremely similar. Pregnant individuals with preexisting diabetes do develop DR during pregnancy, the severity of DR does worsen in a significant number throughout its course, and more evidence is required to truly know its effect on those with type 2 diabetes.

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DRUG TREATMENT

Effectiveness of bevacizumab step therapy for neovascular age-related macular degeneration.

Eye (London, England) 2022 Sep 20

Siktberg J, Kim SJ, Sternberg P Jr, Patel S.

Objective: To determine the effectiveness of bevacizumab step therapy for neovascular age-related macular degeneration (nAMD) in routine clinical practice.

Methods: In this retrospective case series, eyes initiating treatment for nAMD at an academic medical centre from 2011-2019 were included. Exclusion criteria included previous intravitreal anti-VEGF injections, prior non-cataract intraocular surgery, <1 year of treatment, and not starting on monthly bevacizumab therapy. Of 895 eligible eyes, 548 were excluded, yielding 347 eyes in the study population. These eyes were treated for nAMD under the bevacizumab step therapy protocol with an option to switch to another agent in the event of predefined treatment failure. Treatment failure was defined as losing 15 or more Early Treatment Diabetic Retinopathy Study letters or switching to an alternative anti-VEGF agent. Eyes that did not meet these criteria were deemed treatment successes. Annual change in mean VA from baseline (ΔVA) was the primary outcome. Secondary outcomes included treatment success rate, medication switch rate, and post-switch ΔVA.

Results: After 1 year, mean ΔVA was +8.4 letters (95% CI: +6.1 to +10.6 letters). 86% had treatment success, and 6% of eyes had switched to aflibercept. In years 2-7, ΔVA ranged from +7.0 to -0.7 letters, and treatment success rates ranged from 68 to 82%. 11% (n = 38) of eyes were switched to aflibercept. The post-switch ΔVA in these eyes was -7.1 letters (95% CI: -13.3 to -0.1) after a mean of 17.7 ± 12.6 injections over an average of 2.7 ± 2.0 years. CONCLUSION: A bevacizumab step therapy protocol in routine clinical practice is effective for long-term treatment of nAMD.

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Neovascular age-related macular degeneration without exudative recurrence over 24 months after initial remission.

Scientific Reports 2022 Sep 19

Cho HJ, Jeon YJ, Yoon W, Yoon J, Kim J, Kim JW.

We investigated the characteristics of neovascular age-related macular degeneration (AMD), which rarely recurs after initial remission. This study retrospectively analyzed 392 neovascular AMD patients treated with anti-vascular endothelial growth factor (VEGF). All patients received three monthly loading doses of anti-VEGF injections, followed by a pro re nata (as needed) regimen for 24 months. The baseline characteristics associated with the odds of having no recurrence within 24 months were evaluated using multivariate modeling. After the initial three loading injections over 24 months, 58 (14.8%) eyes showed no exudative recurrence and did not require additional anti-VEGF injections. These patients without exudative recurrence had significantly better best-corrected visual acuity (P = 0.003) and lower central subfoveal thickness (P = 0.035) at 24 months than those with exudative recurrence. Additionally, the incidence of macular atrophy was significantly lower in the former than in the latter (8.6% vs. 21.9%; P = 0.020). Multivariate analysis revealed that younger age (odds ratio [OR], 0.901; P = 0.033), smaller lesion size (OR, 0.589; P = 0.016), and absence of fibrovascular pigment epithelial detachment (PED) (OR, 1.349; P = 0.028) were associated with higher odds of no recurrence during follow-up. Approximately 15% of the neovascular AMD patients showed no exudative recurrence after initial remission during the 24-month follow-up. The infrequent recurrence after initial remission correlated with younger age, smaller lesion size, and absence of fibrovascular PED.

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Topographical Analysis of the Choriocapillaris Reperfusion After Loading Anti-VEGF Therapy in Neovascular AMD.

Translational vision science & technology 2022 Sep 1

Viggiano P, Grassi MO, Pignataro M, Boscia G, Borrelli E, Molfetta T, Evangelista F, Alessio G, Boscia F.

Purpose: The purpose of this study was to evaluate choriocapillaris vascular density changes around macular neovascularization (MNV) before and after anti-vascular endothelium growth factor (VEGF) injections by optical coherence tomography angiography (OCTA).

Methods: Treatment-naïve eyes with a diagnosis of exudative AMD and type 1 MNV were included. En face optical coherence tomography angiograms were analyzed for percentage of choriocapillaris (CC) flow deficit percentage (FD%), the FD average area (FDa), and the FD number (FDn) in 5 progressive 200-µm-wide concentric rings (R1, R2, R3, R4, and R5) surrounding the dark halo around the MNV. The OCTA acquisition was performed at the following visits: (i) before the loading phase of

intravitreal injection of aflibercept or ranibizumab (T1), and (ii) 1 month after the last intravitreal injection of loading phase comprising 3 monthly injections (T2).

Results: A total of 30 eyes of 30 Caucasian patients with treatment naïve neurovascular AMD (nAMD) were included in the study. All rings showed a progressive FD% reduction at T2 in comparison to T1 values indicating gradual CC reperfusion of the peripheral rings. Furthermore, we found a progressive contraction of the FD average area in all the rings considered ($P < 0.05$). On the other hand, at T2, a significant increase in the FD number of the 5 rings was displayed, as compared to T1 ($P < 0.05$). CONCLUSIONS: Our analysis showed topographical CC reperfusion after loading anti-VEGF therapy. CC flow deficits were greater around the associated dark halo before treatment, followed by a progressive recovery of CC flow after intravitreal therapy.

Translational relevance: OCTA may be used to assess the development and progression of MNV but also in assessing response to intravitreal injections of anti-VEGF.

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PATHOPHSIOLOGY

In vivo assessment of associations between photoreceptors structure and macular perfusion in type 1 diabetes.

The British Journal of Ophthalmology 2022 Sep 1

Viggiano P, Costanzo E, Giannini D, Fragiotta S, De Geronimo D, Giorno P, Picconi F, Frontoni S, Varano M, Parravano M.

Purpose: To explore the potential relationships between macular vascular network and different adaptive optics (AO) metrics in patients with type 1 diabetes mellitus (DM1) with no signs (NoDR) or mild non-proliferative diabetic retinopathy (NPDR).

Design: Observational cross-sectional study.

Methods: Forty eyes of consecutive patients with DM1 (12 NoDR and 28 NPDR) and 10 healthy age-matched control subjects were included. All patients and controls were imaged using AO retinal camera and PLEX Elite 9000 optical coherence tomography (OCT) angiography (OCTA). The AO outcome measures to evaluate the cone photoreceptor mosaic characteristics were as follows: (1) Cone density (CD); (2) Linear Dispersion Index (LDi) and (3) Heterogeneity Packing Index (HPi). The OCTA outcome measures included: (1) superficial capillary plexus (SCP) perfusion density (PD); (2) deep capillary plexus (DCP) PD and (3) the choriocapillaris (CC) flow deficit percentage (FD%). RESULTS: NPDR group exhibited a close relationship between cone metrics and CC FD. Notably, CC FD% increase along with LDi ($p=0.035$), while the increasing CC FD% were associated with reducing CD ($p=0.042$) and the HPi ($p=0.017$). Furthermore, the OCTA parameters, including PD SCP and DCP, showed a significant negative correlation with CD.

Conclusions: Our results demonstrated the relationship between macular perfusion at both retinal and choroidal levels and the cone mosaic in patients with DM1 interpolating swept-source-OCTA and AO metrics. In NPDR eyes, the photoreceptor damage was accompanied by CC insufficiency since the early stages of the disease.

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DIAGNOSIS AND IMAGING

Reproducibility of macular perfusion parameters in non-proliferative diabetic retinopathy patients by two different OCTA sweep modes.

International Journal of Ophthalmology 2022 Sep 18

Qu S, Rong A, Niu YL, Liu X, Zhang YS, Liu CY, Bi YL.

Aim: To assess the reproducibility of macular perfusion parameters in non-proliferative diabetic retinopathy (NPDR) patients measured by different examiners and two different sweep modes of optical coherence tomography angiography (OCTA).

Methods: Ninety-eight (98 eyes) patients with NPDR were included in this study. All participates were performed three times using Cirrus OCTA with Angiography 3×3 mm2 and 6×6 mm2 sweep mode by two examiners. The macular foveal avascular zone (FAZ) and vessel density (VD) in the superficial retinal layer (SRL) were measured. The reproducibility of the measurements was evaluated with intraclass correlation coefficients (ICC) and coefficient of variation (CoV). RESULTS: The intra-mode ICCs of Angiography 3×3 mm2 and 6×6 mm2 sweep mode were 0.957 to 0.959 and 0.964 to 0.977, respectively; and the inter-mode ICCs were 0.962 to 0.970. The intra-examiner ICCs of macular perfusion parameters were >0.950; and the inter-examiner ICCs were 0.928 to 0.969. All CoVs were <1.0%.

Conclusion: Cirrus OCTA can measure macular perfusion parameters in NPDR patients with excellent reproducibility. The measurements of FAZ and VD in the SRL determined by Angiography 3×3 mm2 and 6×6 mm2 sweep mode are highly consistent and both sweep modes are suitable for macular perfusion parameters measurement.

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PATIENT OUTCOMES

Long-term persistence with aflibercept therapy among treatment-naïve patients with exudative age-related macular degeneration in a universal health care system: a retrospective study.

BMC Ophthalmology 2022 Sep 19

Angermann R, Franchi A, Frede K, Stöckl V, Palme C, Kralinger M, Zehetner C.

Background: This study aimed to analyse the persistence rates of treatment-naïve patients with neovascular age-related macular degeneration (nAMD) who received intravitreal aflibercept therapy in a universal health care system.

Methods: In this single-centre retrospective cohort study, we audited data of 918 treatment-naïve patients who received exclusively intravitreal aflibercept therapy for nAMD between September 2015 and May 2021. The primary outcome measures were the rates of treatment nonpersistence (gap in ophthalmological care > 6 months) and long-term nonpersistence (> 12 months).

Results: The rates of nonpersistence and long-term nonpersistence were 12.3% and 3.4% after one year; 22.4% and 9.5% after two years; and 38.3% and 19.3% after five years, respectively. Logistic regression analysis revealed that older age (p = 0.045), male sex (p = 0.039), requirement for caretakers or ambulance (p = 0.001), and low visual acuity of the study eye (p = 0.010) or fellow eye (p = 0.029) were independent risk factors for long-term nonpersistence. Patients aged > 80 and > 85 years (p = 0.013 and p = 0.022, respectively) had more than twice the risk for being nonpersistent to therapy within two years of follow-up compared with younger patients. Male patients (p = 0.033), patients requiring a caretaker (p = 0.038), and patients living > 60 km from the clinic (p = 0.029) had a 2 × higher risk of being persistently nonpersistent to therapy.

Conclusions: Patients with nAMD who were treated with aflibercept had lower nonpersistence rates than those reported in current literature. Multiple independent risk factors were correlated with long-term nonpersistence, early nonpersistence, or complete loss to follow-up. Considering the possible consequences of reduced compliance, further strategies are urgently needed for patients at risk of nonpersistence to therapy.

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CASE REPORTS

Cat scratch disease: What to do with the cat?

American Journal of Ophthamology Case Reports 2022 Sep 9

Okrent Smolar AL, Breitschwerdt EB, Phillips PH, Newman NJ, Biousse V.

Purpose: Cat scratch disease (CSD) frequently has ophthalmologic manifestations. The ophthalmologist's approach to treating neuroretinitis is familiar, but few eye care providers are comfortable answering the next question of "what do I do with my cat?" Published guidelines are often vague in answering the complexities of real-life conundrums that can lead patients and their doctors to believe that risk mitigation should involve removal of the animal. Here, we present demonstrative scenarios informed by clinical practice and provide updated recommendations.

Observations: A 10-year-old boy presented with reduced vision in the right eye. Funduscopic examination identified optic nerve head edema with subretinal fluid, and a macular star developed one week later, consistent with the diagnosis of neuroretinitis. Serology confirmed Bartonella henselae antibodies and a diagnosis of CSD. The father disclosed that the family has recently adopted three kittens, who have scratched the boy and the patient's younger sister. The physician and patient's family find themselves at a loss regarding best practices for what should be done with the kittens.

Conclusions and importance: B. henselae has been detected in a variety of mammals and can be transmitted via vectors such as fleas. Even well-appearing animals can transmit the bacteria, months to years after their initial infection. Symptoms, clinical and laboratory findings will depend on bacterial load and strain virulence, as well as the physiological/immunological status of the host, with people at the extremes of age and the immunocompromised being at greater disease risk. Flea control is crucial to minimize transmission risk. Our veterinary expert (EBB) recommends testing (with serology and PCR) and treating infected animals (with doxycycline and a quinolone). Patients should be counseled to speak with their pets' veterinarian. When addressing the concerns of our CSD patients in clinical practice, ophthalmologists should be aware of the strategies for minimizing Bartonella transmission risk, and cognizant of the One Health approach for managing zoonoses.

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REVIEW

Efficacy and safety of brolucizumab in age-related macular degeneration: A systematic review of real-world studies.

Acta Ophthalmologica 2022 Sep 8

Baumal CR, Sørensen TL, Karcher H, Freitas RL, Becher A, Balez S, Clemens A, Singer M, Kodjikian L.

Intravitreally injected anti-vascular endothelial growth factor (anti-VEGF) agents are first-line treatment for neovascular age-related macular degeneration (nAMD). Phase 3 trials demonstrated non-inferiority of anti-VEGF therapy with brolucizumab compared with aflibercept in best corrected visual acuity (BCVA) gains, with superior anatomical outcomes after brolucizumab. The purpose of the review was to summarize real-world efficacy and safety data on brolucizumab in patients with nAMD. The review protocol was registered with PROSPERO (ID: CRD42021290530). We conducted systematic searches in Embase, Medline and key ophthalmology congress websites (19 October 2021). Original reports of efficacy and/or safety in patients receiving brolucizumab to treat nAMD in clinical practice were eligible. The descriptive summary includes reports describing at least 10 brolucizumab-treated eyes. In total, 2907 brolucizumab-treated eyes from 26 studies were included. Outcomes were available for treatment-naive eyes (six studies), eyes switched to brolucizumab from other anti-VEGFs (16 studies), and/or treatment-naive and switch eyes combined (eight studies). Follow-up time points ranged from 4 weeks to 1 year post-brolucizumab initiation. For BCVA, significant improvements compared with brolucizumab initiation were reported in four of six studies in treatment-naive eyes (mean BCVA improvement, range: +3.7 to +11.9 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and in three of 12 studies in switch eyes (range: +9.0 to +15 ETDRS letters) (all $p < 0.05$); remaining studies reported no significant post-brolucizumab BCVA changes. For central subfield thickness (CST), improvements post-brolucizumab initiation were reported in all six studies in treatment-naive eyes (mean CST improvement, range: -113.4 to -150.1 µm) and in eight of 11 studies in switch eyes (range: -26 to -185.7 µm) (all $p < 0.05$). The 14 studies reporting on intraretinal, subretinal and/or total fluid observed improvements post-brolucizumab initiation. The four studies comparing treatment intervals observed extension of the interval between injections after switching to brolucizumab from other anti-VEGFs. Incidence of intraocular inflammation ranged from 0% to 19%. In conclusion, real-world efficacy and safety data concur with brolucizumab pivotal trials. Additionally, reduction of disease activity in anti-VEGF switch eyes was demonstrated by fluid reduction and/or visual acuity gain, along with prolongation of the interval between injections.

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