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Setting Priorities for Diabetic Retinopathy Clinical Research and Identifying Evidence Gaps

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Purpose: Prioritizing comparative effectiveness research may contribute to obtaining answers that clinicians perceive they need and may minimize research that could be considered wasteful. Our objective was to identify evidence gaps and set priorities for new systematic reviews and randomized controlled trials for managing diabetic retinopathy (DR), including diabetic macular edema (DME).

Design: Cross-sectional study.

Participants: Diabetic Retinopathy Clinical Research Network (DRCR.net) investigators.

Methods: We provided recommendations from the American Academy of Ophthalmology's 2012 Preferred Practice Patterns for Diabetic Retinopathy as 91 answerable clinical research questions about intervention effectiveness to 410 DRCR.net investigators to rate each question's importance from 0 (not important) to 10 (very important) using a 2-round Delphi survey and to suggest additional questions. We considered questions as high priority if at least 75% of respondents to both rounds assigned an importance rating of 5 or more in round 2. We also extracted outcome measures relevant to DR and asked respondents to identify those that must be measured in all studies. We mapped Cochrane reviews published up to March 2016 to high-priority clinical research questions.

Main Outcome Measure: Ranking of importance of each clinical question.

Results: Thirty-two individuals completed rounds 1 and 2 and suggested 15 questions. Among the final list of 106 clinical research questions, 22 questions met our definition of high priority: 9 of 22 concerned the effectiveness of anti-VEGF therapy, and 13 of 22 focused on how often patients should be followed up (re-examination) and treatment effectiveness in patients with specific characteristics (e.g., DME). Outcomes that 75% or more of respondents marked as "must be measured in all studies" included visual acuity and visual loss, death of participants, and intraocular pressure. Only 1 prioritized question was associated with conclusive evidence from a Cochrane systematic review.

Conclusions: A limited response rate among DRCR.net members identified 22 comparative effectiveness research questions as high priority for the management of DR, including DME, but few were associated with Cochrane reviews. These results support the need of systematic reviews and randomized controlled trials to address evidence gaps.

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Two Doses of Intravitreal Ziv-Aflibercept versus Bevacizumab in Treatment of Diabetic Macular Edema: A Three-Armed, Double-Blind Randomized Trial

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Purpose: To compare the efficacy of 2 doses of intravitreal ziv-aflibercept (IVZ) with intravitreal bevacizumab (IVB) in the treatment of center-involved diabetic macular edema (DME) at 12 weeks.

Design: Three-armed, double-blind, randomized clinical trial.

Participants: Eyes with center-involved DME.

Methods: In this trial, 123 eyes with DME were randomly assigned to 3 injections of 1.25 mg IVZ, 2.5 mg IVZ, and 1.25 mg IVB every 4 weeks. Complete ophthalmologic examination and central macular thickness (CMT) measurement by optical coherence tomography were performed every 4 weeks up to 12 weeks.

Main Outcome Measures: Change in best-corrected visual acuity (BCVA) at 12 weeks.

Results: Although no significant difference was evident between the 2 ziv-aflibercept groups at 12 weeks, the BCVA change was significantly better in the ziv-aflibercept 1.25 mg group than in the IVB group at the 12-week visit ($P = 0.021$). In regard to CMT changes, there was no significant difference between the 2 ziv-aflibercept groups; however, a significantly greater reduction in CMT was observed in the ziv-aflibercept 2.5 mg group compared with the IVB group at 12 weeks ($P = 0.037$). Subgroup analysis disclosed no difference in BCVA outcomes at 12 weeks among the groups in the eyes with baseline BCVA $\geq$20/50. In the eyes with baseline BCVA $<$20/50, the improvement was significantly better at 12 weeks in the ziv-aflibercept 1.25 mg group compared with the IVB group ($P = 0.011$).

Conclusions: The 12-week results of this trial disclosed that both 1.25 mg and 2.5 mg doses of IVZ and IVB demonstrated BCVA improvement over baseline in the treatment of center-involved DME. However, a stronger effect of IVZ compared with IVB in terms of both visual acuity improvement and macular thickness reduction was detected in the eyes with initial BCVA $<$20/50. Longer-term efficacy and safety data will be needed to understand the role for this drug in practice.

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A 24-Month Evaluation of Aflibercept for Wet Age-Related Macular Degeneration in Patients Previously Receiving Ranibizumab or Bevacizumab

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Purpose: To report the 24-month results and predictive factors for outcomes in patients transitioned from other anti−vascular endothelial growth factor agents to aflibercept for the treatment of exudative age-related macular degeneration (AMD).

Design: A prospective, single arm, investigator-initiated study.

Participants: A total of 24 patients participated in the study and 87.5% (n = 21) completed the 24 month assessments. Patients were included if they had an active exudative AMD confirmed by fluorescein angiography, presence of fluid on spectral-domain optical coherence tomography (OCT) or new hemorrhage on clinical examination, Electronic Early Treatment Diabetic Retinopathy Study vision of 25 to 80 letters (Snellen equivalent of approximately 20/25−20/320), prior bevacizumab or ranibizumab injections within 3 months of enrollment, and an initial response on OCT defined as a decrease of retinal edema and/or subretinal fluid to anti−vascular endothelial growth factor injections.

Methods: Patients were treated the first 3 months with 2 mg of intravitreal aflibercept monthly, followed by a fixed bimonthly schedule for 24 months. At each study visit, visual acuity and a spectral-domain OCT scanning of both eyes were performed.

Main Outcome and Measures: The mean absolute change from baseline in central subfield thickness at month 24, mean change from baseline in best-corrected visual acuity (BCVA) score, change from baseline in macular volume, and cube average thickness by spectral-domain OCT. Additionally, predictive factors associated with final visual and anatomic outcomes at month 24.

Results: A mean decrease in central subfield thickness of −41 μm ($P = 0.004$) was observed with a mean increase in ETDRS BCVA of +10.4 letters ($P < 0.001$). At study entry, BCVA was a significant predictive factor for BCVA change at month 24 (rho = −0.59; $P = 0.003$). Also, the duration between AMD diagnosis and study entry was a significant factor for central subfield thickness change at month 24 (rho = −0.51; $P = 0.011$).

Conclusions: In nonnaïve patients with active exudative AMD, treatment with a fixed intravitreal aflibercept dosing regimen for 24 months demonstrated sustained improvements in anatomy and vision in patients transitioned from other anti−vascular endothelial growth factor agents and stability when compared with 12-month outcomes. Patients who benefited most were those with worse vision at entry and longer duration of disease.

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Treat-and-Extend Regimen for Macular Edema Secondary to Central Retinal Vein Occlusion: 12-Month Results

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Purpose: To determine treatment outcomes after 12 months of bevacizumab and ranibizumab therapy using a treat-and-extend regimen in patients with macular edema resulting from central retinal vein occlusion (CRVO).

Design: Retrospective, interventional, consecutive case series.

Methods: Sixty eyes of 58 patients diagnosed with CRVO and associated macular edema between May 2010 and June 2014 were included. Eyes were treated with bevacizumab and/or ranibizumab for a minimum of 1 year, using a treat-and-extend regimen.

Main Outcome Measures: Outcome measures were change from baseline visual acuity (VA), proportion of eyes gaining/losing ≥3 VA lines, change from baseline central retinal thickness (CRT), mean number of injections administered, and the longest treatment-free interval attained between injections.

Results: At baseline, mean logMAR VA was 1.18±0.71 (Snellen equivalent: 20/302), which improved to 0.85±0.71 (Snellen equivalent: 20/142) after 12 months of therapy ($P = 0.018$). During this period, 44.9% of eyes had gained ≥15 letters, while 10.2% had lost ≥15 letters. The mean CRT improved from 564.7±219.3 μm at baseline to 302.8±115.8 μm at 12-month follow-up ($P < 0.001$). Patients received, on average, 8.1 injections during the first year of treatment, and the mean longest duration of successful extension between injections during year 1 was 9.3±4.4 weeks. Multivariable analyses revealed that change in CRT over the first 3 months of therapy was significantly associated with the ability to extend injection intervals to at least 8 weeks' duration ($P < 0.05$).

Conclusions: The treat-and-extend regimen is effective in achieving visual and anatomic improvements in patients with macular edema secondary to CRVO through the first year of therapy. Change in CRT during the first 3 months of treatment may help predict which patients will respond more favorably to an extension phase at or beyond 8 weeks.

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Projection Artifact Removal Improves Visualization and Quantitation of Macular Neovascularization Imaged by Optical Coherence Tomography Angiography

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Purpose: To visualize and quantify the size and vessel density of macular neovascularization (MNV) using optical coherence tomography angiography (OCTA) with a projection artifact removal algorithm.

Design: Multicenter, observational study.

Participants: Subjects with MNV in ≥1 eye.

Methods: Patients were imaged using either a swept-source OCTA prototype system or a spectral-domain OCTA prototype system. The optical microangiography (OMAG) algorithm was used to generate the OCTA images. Projection artifacts from the overlying retinal circulation were removed from the OMAG OCTA images using a novel algorithm. After removal of the projection artifacts from the OCTA images, we assessed the size and vascularity of the MNV. Concurrent fluorescein angiography and indocyanine green angiography images were used to validate the artifact-free OMAG images whenever available.

Main Outcome Measures: Size and vascularity of MNV imaged with OCTA before and after the use of a projection-artifact removal algorithm.