7/15/2022 02:15 pm

Diabetic Retinopathy 2 Symposium

Association of Predominantly Peripheral Lesions on Ultra-Widefield Imaging and the Risk of DR Worsening Over Time: Results of DRCR Retina Network Protocol AA

- Dennis Marcus, MD

Objective:
Can the assessment of risk of retinopathy worsening or treatment be improved by the detection of predominantly peripheral DR lesions (PPL) outside the standard ETDRS 7 fields on UWF imaging?

Purpose:
Compared with standard ETDRS 7 fields, ultrawide field (UWF) imaging has the improved ability to identify peripheral diabetic retinopathy (DR) lesions. However, it is unknown whether the detection of predominantly peripheral lesions (PPL) can better predict the risk of disease worsening (i.e., retinopathy worsening or treatment) over time beyond the risk associated with baseline ETDRS DR severity scale (DRSS) level

Methods:
A total of 544 study eyes with nonproliferative DR (NPDR) from 367 participants were enrolled in a prospective multicenter longitudinal observational study conducted by DRCR Retina Network. Study participants were at least 18 years old with type 1 or 2 diabetes. Follow-up visits occurred annually for 4 years. 200° UWF color and fluorescein angiography (FA) images were collected through 4 years. DR severity and PPL on UWF-color (color-PPL) and UWF-FA (FA-PPL) were evaluated at a centralized reading center. PPL was defined as DR lesions with a greater extent outside versus inside the standard ETDRS fields. Initiation of treatment for DR and/or DME was at investigator discretion. The primary outcome was disease worsening over 4 years, defined as 2 or more steps DRSS worsening within ETDRS fields on UWF-color images or receipt of DR treatment.

Results:
Over 4 years, disease worsening was observed in 45% of eyes with mild NPDR at baseline, 40% with moderate NPDR, 26% with moderately-severe NPDR, and 43% with severe NPDR. Baseline PPL were present in 41% of eyes on UWF-color and 46% of eyes on UWF-FA. Rates of disease worsening did not differ by baseline color-PPL (38% when present vs 43% when absent; HR, 0.78; 95% CI, 0.57-1.07; $P = .13$) but differed by baseline FA-PPL (50% when present vs 31% when absent; HR, 1.72; 95% CI, 1.25-2.36; $P < .001$).

Conclusion:
Independent of baseline DRSS, FA-PPL were associated with greater risk of disease worsening over 4 years while color-PPL were not. These results suggest that for eyes with NPDR, a more accurate prediction of the risk for future disease worsening may be achieved by incorporating UWF-FA findings into DR staging systems.

IRB APPROVAL Yes

7/15/2022 02:19 pm

Diabetic Retinopathy 2 Symposium

Utilization, Payments, and Effectiveness of Teleophthalmology for Remote Diabetic Eye Screening in the US

- Parisa Emami Naeini, MD, MPH
- Monica Lieng, PhD
- Sophie Lee
- Susan Alber, PhD
- Neesurg Mehta, MD
- Glenn Yiu, MD, PhD

Objective:
Can remote retinal imaging result in earlier access to eye care in patients with diabetes?

Purpose:
To evaluate trends in utilization, insurance coverage, and effectiveness of remote retinal imaging for improving access to eye screening in diabetic patients in the U.S. over the past decade

Methods:
We used the OptumLabs® Data Warehouse (OLDW) – a comprehensive, real-world database of de-identified administrative claims for commercial insurance and Medicare Advantage enrollees in the U.S.. We analyzed utilization and insurance payments for all claims between 2011-2020 using Current Procedural Terminology (CPT) codes for teleretinal screening (remote retinal imaging 92227 or 92228, or fundus photography 92250 by non-eyecare providers). Finally, we compared the time to initial eye screening using teleophthalmology or in-person eye care visits among newly-diagnosed type 2 diabetic patients with at least 1 year of continuous enrollment.

Results:
Teleophthalmology utilization increased from 11,603 claims in 2011 to 33,392 claims in 2020, but the proportion of claims paid decreased from 88% in 2011 to 47% in 2020 and were lower for Medicare Advantage compared to commercial insurance enrollees. The decline in insurance coverage disproportionately impacted patients over age 65, women, Blacks, and those with lower household income. The mean (SD) inflation-adjusted amounts for codes 92227 and 92228 remained relatively unchanged from $12.38 ($14.54) to $14.85 ($7.15) for 92227 and from $19.31 ($9.04) to $25.10 ($10.74) for 92228, while payments for CPT 92250 increased from $45.15 ($36.17) in 2011 to $64.70 ($37.38) in 2020. Among 968,846 patients with newly-diagnosed diabetes who were continuously enrolled for at least 1 year, 5,459 (0.6%) patients underwent remote eye imaging and 208,023 (27%) underwent an in-person eye visits. The median time (95% CI) to screening was 2.0 (0-10.9) months for remote imaging and 3.4 (0-11.0) months for in-person visits. Interestingly, when same-day screenings were excluded, median time to screening with remote and in-person exams were 4.1 months (0.2-11.3) and 4.3 months (0.3-11.1), respectively.

Conclusion:
Teleophthalmology using remote retinal imaging provides earlier access to eye care among patients with newly diagnosed diabetes by increasing rates of same-day screenings. While utilization has increased over the past 10 years, insurance coverage has decreased, however, disproportionately impacting vulnerable populations, and posing substantial barriers against widespread adoption.

IRB APPROVAL

7/15/2022 02:23 pm

Diabetic Retinopathy 2 Symposium

New Tool for Predicting the 3-Year Risk of Vision-Threatening Diabetic Retinopathy in Patients With Type 2 Diabetes Mellitus

- Bobeck Modjtahedi, MD
- Jun Wu, MD, MS
- Tiffany Luong, MPH
- Jose Pio, MD, MPH
- Donald Fong, MD, MPH
- Alicia Menezes, MD
- Vincent Garmo, MHS
- Wansu Chen, PhD

Objective:
To develop risk prediction models for the future risk of new-onset vision-threatening diabetic retinopathy (VTDR) in patients with type 2 diabetes mellitus.

Purpose:
The ability to predict future VTDR would allow for more targeted monitoring and intervention to prevent vision loss.

Methods:
In this retrospective cohort study, patients ≥18 years old who underwent diabetic retinopathy screening in 2012-2015 without a history of diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), macular exudative or retinal vascular disease, as well as vitreoretinal treatment were identified. A total of 215,154 patients met eligibility criteria. More than 20 potential predictors of VTDR were extracted and considered. VTDR was defined as DME and/or PDR based on diagnosis codes with a concurrent retinal intervention. Prediction models for the 3-year risks of VTDR, DME, and PDR were developed and validated. Imputation datasets was split into two: records from 11 medical service areas were used for validation and training while two medical service area were used for testing. A two-step approach was taken to develop the most parsimonious model with optimal predictive power. First, a cross-validated LASSO regression model was generated to preselect potentially important features. The pre-selected features were then forwarded to a second step, in which each pre-selected feature was added sequentially to maximize c-index until the increase in c-index was less than 0.01. The models that appeared most often were selected as the final models.

Results:
The final cohort of 215,154 patients had a mean age of 60 years and was 54% female, 32% White, and 40% Hispanic. The final models contained diabetic retinopathy status and hemoglobin A1c for all the clinical outcomes. Although other variables such as renal function and duration of diabetes were statistically significantly associated with the outcomes, their inclusion did not improve the c-index sufficiently to be included in the final model. The average c-index pooled over the 50 validation datasets and 10 testing datasets were ≥ 92% and 94% for each outcome at 3 years, respectively. Figure 1 provides a heatmap of the predicted risks of each outcome: for each retinopathy severity, users can take a patient's hemoglobin A1c to identify the predicted risk of an outcome based on the color key on the right of each image with warmer/more red colors representing a higher risk. A risk calculator is available at https://vtdr.kp-scalresearch.org/

Conclusion:
The future risk of new-onset VTDR, DME, and PDR can be accurately predicted using retinopathy status and hemoglobin A1c. These models may be utilized to assist patient education and management, including determining follow-up schedules and identifying patients who may benefit from more rigorous diabetes control and/or prophylactic ophthalmic treatment.

IRB APPROVAL Yes

Figure 1. Heatmaps for the predicted 3-year risk of VTDR, DME, and PDR.

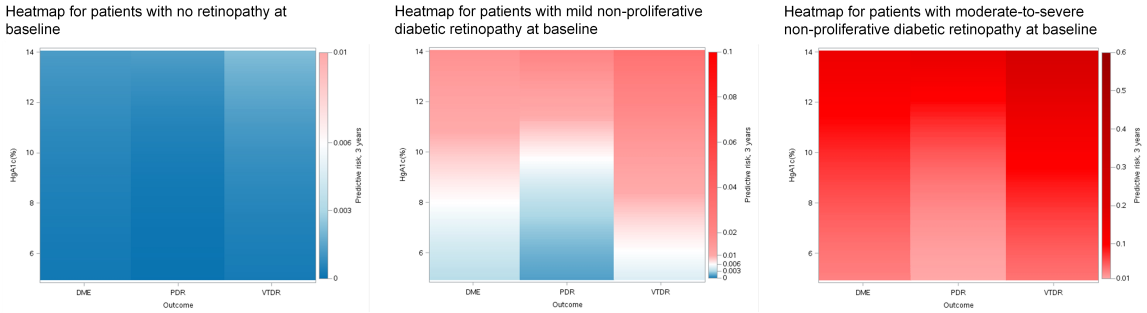

Figure 1: Heatmaps for the predicted 3-year risk of VTDR, DME, and PDR

7/15/2022 02:27 pm

Diabetic Retinopathy 2 Symposium

Long-Term Real-World Treatment Patterns Among Patients With Diabetic Macular Edema Initiating Anti-VEGF: 6-year Follow-up Using the IRIS Registry

- Theodore Leng, MD, MS, FASRS
- Vincent Garmo, MHS
- David Tabano, PhD
- Eunice Kim
- Blanche Kuo, BS
- Meghan Hatfield, MPH
- Andrew LaPrise
- Rishi Singh, MD

Objective:
To understand long-term utilization of anti-VEGF therapy and other related treatments in patients with diabetic macular edema.

Purpose:
This study aimed to characterize long-term treatment patterns including discontinuations, and switching of anti-VEGF therapies amongst patients with diabetic macular edema (DME) from a large ophthalmology registry.

Methods:
A retrospective analysis was performed in treatment-naïve DME patients (no prior anti-vascular endothelial growth factor (anti-VEGF) intravitreal therapy [IVT] in the past 12 months) initiating IVT from 1/1/2015-12/31/2019 using a de-identified electronic medical records registry (IRIS® Registry). Anti-VEGF agent utilization patterns, including agent type, switches (defined as ≥3 consecutive injections of a different anti-VEGF agent from the original agent), and discontinuations (defined as no anti-VEGF IVT for ≥12 months). Results were stratified by baseline visual acuity (VA) and initial anti-VEGF agent including on-label (ranibizumab and aflibercept) and off-label agent (bevacizumab).

Results:
Of 190,345 eyes (147,687 patients), 147,336 eyes (77%) received only 1 anti-VEGF agent over a mean follow-up of 2.3 years, with bevacizumab being the most commonly used agent (53% of eyes) followed by aflibercept (21%) and ranibizumab (11%). Bevacizumab use decreased by a mean of 5.6% each year and on-label agent use increased by a mean of 6.9% each year (**Figure 1**). 15% of eyes switched anti-VEGF agents after a mean of 53 weeks. Of these switches, 74% switched from bevacizumab to an on-label agent after a mean of 50 weeks, and 10% switched from an on-label agent to bevacizumab after a mean of 65 weeks. 52% of eyes discontinued anti-VEGF treatment after a mean of 24 weeks, of which 33% reinitiated after a mean of 91 weeks. Rates of discontinuation, switching, and reinitiation were similar regardless of baseline VA, though discontinuation with no reinitiation of IVT during follow-up was highest in patients with VA ≤20/200 at baseline (**Figure 2**).

Conclusion:
Although a majority of patients with DME discontinue IVT therapy after a mean of 6 months, a third reinitiated. 58% patients initially received bevacizumab, but its use decreased over time with an increased use of on-label agents. Reasons for switching and discontinuation should be further explored.

IRB APPROVAL No - no IRB or exemption

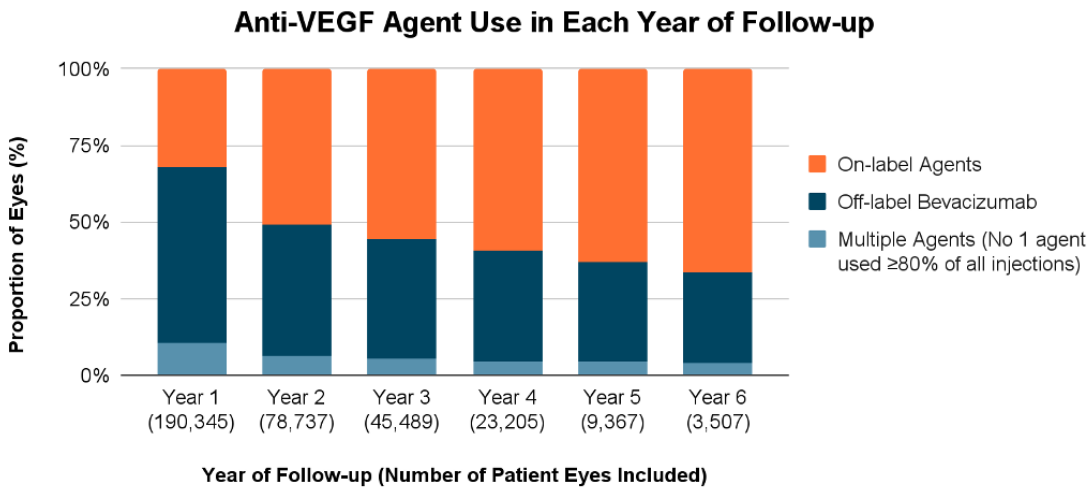

Figure 1. Anti-VEGF agent use in each year of follow-up

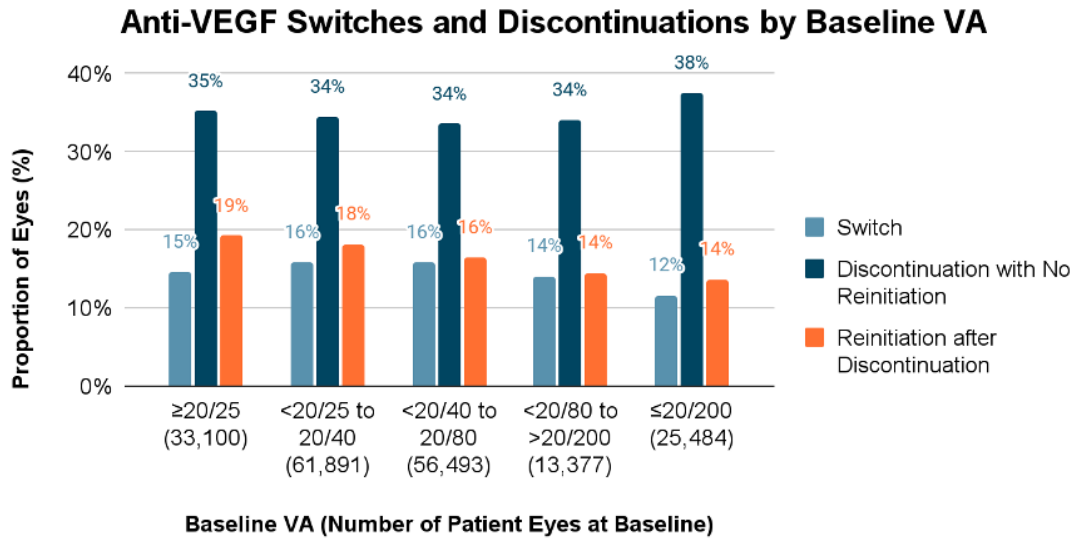

Figure 2. Anti-VEGF switching and discontinuation by baseline VA

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Diabetic Retinopathy 2 Symposium
Suprachoroidal Delivery of RGX-314 Gene Therapy for Diabetic Retinopathy: Phase II ALTITUDE Study

- Charles Wykoff, MD, PhD, FASRS

Objective:
To evaluate the safety, tolerability, and efficacy of RGX-314 by suprachoroidal delivery in patients with Diabetic Retinopathy (DR) without Center-Involved Diabetic Macular Edema (CI-DME).

Purpose:
In eyes with severe non-proliferative DR (NPDR), anti-VEGF therapy by repeated intravitreal bolus injections has been demonstrated to improve DR severity scores and reduce the development of vision threatening complications; in order to maintain optimal anatomic outcomes, however, multiple injections appear to be required. RGX-314 is a gene therapy that utilizes an AAV8 vector to deliver a transgene for a soluble anti-VEGF fab designed to provide continuous anti-VEGF therapy following a single treatment. ALTITUDE is evaluating RGX-314 delivered into the suprachoroidal space (SCS) through an in-office procedure.

Methods:
ALTITUDE is an open-label, randomized, dose-escalation trial evaluating the efficacy, safety and tolerability of suprachoroidal delivery of RGX-314 using the SCS Microinjector® in patients with a DR diagnosis of moderately severe or severe nonproliferative DR (NPDR) or mild proliferative DR (PDR). 20 patients in Cohort 1 were randomized to receive RGX-314 at a dose level of $2.5x10^{11}$ genomic copies per eye (GC/eye) versus observational control at a 3:1 ratio. Additional cohorts will include 40 patients randomized to receive RGX-314 at a dose level of $5x10^{11}$ GC/eye, in which enrollment is ongoing. The primary outcome is the proportion of eyes with 2-step improvement in DR severity scale (DRSS) score at 48 weeks. Secondary outcomes include safety as well as development and intervention for DR-related complications.

Results:
As of September 29, 2021, RGX-314 was well tolerated in 15 patients in Cohort 1. One unrelated serious adverse event was reported in the fellow eye of an RGX-314 patient. One case of mild episcleritis resolved with topical corticosteroids, and no intraocular inflammation was observed. Common ocular treatment emergent adverse events in the study eye were not considered drug-related and were predominantly mild. 5 of the 15 patients (33%) demonstrated a 2-step or greater improvement in DRSS score from baseline at three months, compared to 0 of the 5 patients (0%) in the observational control group. In the 7 patients who had NPDR (DRSS 47-53) at baseline, 3 patients (43%) demonstrated a 2-step or greater improvement at three months.

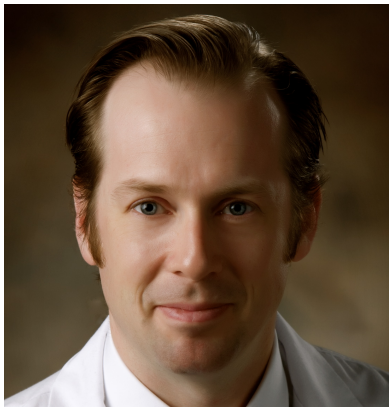
Conclusion:
RGX-314 gene therapy has the potential to provide sustained clinical outcomes in the treatment of diabetic retinopathy with a one-time suprachoroidal treatment that is administered in-office.

IRB APPROVAL Yes

7/15/2022 02:47 pm

Diabetic Retinopathy 2 Symposium

Personalized Treatment Interval Dosing Dynamics Over 2 Years in the Phase 3 YOSEMITE and RHINE Trials of Faricimab in Diabetic Macular Edema



- John Kitchens, MD
- Caroline Baumal, MD
- Glenn Jaffe, MD
- Bianca Gerendas, MD, MSc, PhD
- Francis Abreu, PhD
- Kemal Asik, PhD
- Acner Camino, PhD
- Nitin Jain, MS
- Zdenka Haskova, MD, PhD

Objective:
This study sought to evaluate the durability of faricimab in patients with diabetic macular edema (DME) and present case studies of PTI dosing in the phase 3 YOSEMITE/RHINE trials.

Purpose:
Dual inhibition of the angiopoietin-2 and vascular endothelial growth factor (VEGF)-A pathways with faricimab may extend treatment durability beyond current anti-VEGF therapies for DME. The PTI algorithm in YOSEMITE/RHINE was a protocol-driven treat-and-extend regimen, designed to test the durability of faricimab by tailoring treatment intervals to individual patient response.

Methods:
YOSEMITE (NCT03622580) and RHINE (NCT03622593) were randomized, double-masked, active comparator–controlled trials of faricimab in DME. Patients were randomized 1:1:1 to faricimab 6.0 mg per PTI after a minimum of 4 initial every-4-week (Q4W) doses, faricimab 6.0 mg Q8W after 6 initial Q4W doses, or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. In the PTI arms, patients received faricimab Q4W until central subfield thickness (CST) < 325 µm was achieved at or after week 12. Once achieved, treatment intervals could be extended by 4 weeks (up to Q16W), maintained, or reduced by 4 or 8 weeks (as low as Q4W), based on CST and best-corrected visual acuity change at active dosing visits. Treatment intervals in the faricimab PTI arms were assessed through week 100.

Results:
Of the 1891 patients enrolled in YOSEMITE (N = 940) and RHINE (N = 951), 313 and 319 patients, respectively, were randomized to the faricimab PTI arms. At week 52, > 50% of patients in the PTI arms achieved Q16W dosing and > 70% achieved Q12W dosing or longer. Approximately two-thirds of patients achieved Q12W or Q16W dosing without an interval reduction below Q12W through week 52 (YOSEMITE, 68%; RHINE, 64%). The majority of patients who rapidly achieved Q16W dosing at week 32 (ie, the first timepoint that a patient could be extended to Q16W dosing) subsequently completed a full Q16W dosing cycle and remained on Q16W dosing at week 52. Faricimab PTI dosing dynamics through week 100 and illustrative case studies will be presented at the meeting.

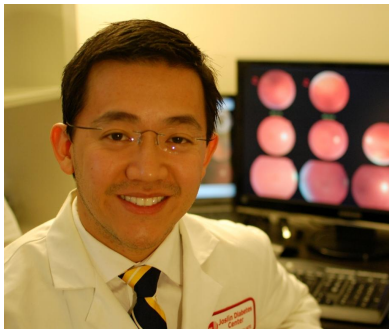
Conclusion:
Representative cases and images from YOSEMITE/RHINE showed that treat-and-extend–based PTI dosing was effectively used to optimize faricimab treatment intervals according to the heterogeneous needs of patients with DME.

IRB APPROVAL Yes

7/15/2022 02:53 pm

Diabetic Retinopathy 2 Symposium

Association of Ultra-Widefield Fluorescein Angiography-identified Retinal Nonperfusion With Risk of Diabetic Retinopathy Worsening Over Time



- Paolo Antonio Silva, MD

Objective:
How does retinal nonperfusion identified on ultrawide field fluorescein angiography relate to risk of future diabetic retinopathy worsening or treatment?

Purpose:
Imaging advances allow the ability to capture posterior and peripheral retinal nonperfusion (NP) on ultrawide field fluorescein angiography (UWF-FA). However, the relationship between peripheral UWF-FA abnormalities and posterior pole pathology and retinopathy worsening or treatment is unclear. This secondary analysis evaluated whether extent and location of retinal NP identified on UWF-FA were associated with diabetic retinopathy (DR) worsening or treatment over time.

Methods:
In a prospective multicenter longitudinal observational study conducted by DRCR Retina Network, 508 eyes with non-proliferative DR and gradable NP on UWF-FA at baseline were analyzed. 200° UWF-color and UWF-FA images were collected at each annual visit through 4 years. A centralized reading center evaluated DR severity scale (ETDRS DRSS) level within ETDRS fields on UWF-color images, as well as NP area (NPA), NP index (NPI), and presence of predominantly peripheral lesions on UWF-FA (FA-PPL). Treatment of DR and/or DME was at investigator discretion. The primary outcome was disease worsening over 4 years, defined as ≥2 steps DRSS worsening within ETDRS fields on UWF-color images or receipt of treatment for DR.

Results:
Adjusting for baseline ETDRS DRSS, the risk of disease worsening over 4 years was higher among eyes with greater overall NPI (HR for 0.1-unit increase, 1.11; 95% CI, 1.02-1.21; $P = .02$). Increasing NPI within the posterior pole (HR, 1.35; 95% CI, 1.17-1.56; $P < .001$) and mid-periphery (HR, 1.08; 95% CI, 1.01-1.16; $P = .04$) were also associated with a higher risk of disease worsening. In a multivariable model with adjustment for baseline ETDRS DRSS and systemic risk factors including diabetes duration, hemoglobin A1c and albuminuria, greater NPI (HR, 1.11; 95% CI, 1.02-1.21; $P = .02$) and presence of FA-PPL (HR, 1.86; 95% CI, 1.34-2.58; $P < .001$) remained significantly associated with disease worsening.

Conclusion:
This study has demonstrated the association of disease worsening with baseline retinal NP and FA-PPL on UWF-FA, even after adjusting for baseline ETDRS DRSS and known systemic risk factors. These results suggest the importance of UWF-FA for predicting disease worsening and support the increased use of UWF-FA to complement color fundus photography for clinical care and research.

IRB APPROVAL Yes

7/15/2022 02:57 pm

Diabetic Retinopathy 2 Symposium

Treat-and-Extend vs Alternate Dosing Strategies With Anti-VEGF Agents to Treat Center-Involving Diabetic Macular Edema: Meta-Analysis of Trials

- Varun Chaudhary, MD
- Gurkaran Sarohia, MD
- Keean Nanji, MD
- Mohammad Khan, MD (c), MSc
- Muhammad Khalid, BSc
- Daniel Rosenberg, MD
- Deven Deonarain, BSc
- Mark Phillips, PhD
- Lehana Thabane
- Peter Kaiser, MD FASRS
- Sunir Garg, MD, FACS, FASRS
- Sobha Sivaprasad, FRCOphth
- Charles Wykoff, MD, PhD, FASRS

Objective:
To comprehensively review the literature assessing anti-vascular endothelial growth factor (anti-VEGF) treatment using a treat & extend (T&E) paradigm versus an alternative dosing paradigm (fixed or PRN) at 12 and 24 months for centre involving diabetic macular edema (CI-DME).

Purpose:
Anti-vascular endothelial growth factor (Anti-VEGF) agents are the standard of care for treating center-involving diabetic macular edema (CI-DME). They are administered using several treatment protocols, including fixed, pro re nata (PRN) and treat-and-extend (T&E) regimens. Due to the lack of evidence around an ideal treatment paradigm, this review systematically compared T&E with fixed and PRN regimens.

Methods:
Ovid MEDLINE, Ovid EMBASE, and CENTRAL were searched. The primary outcome was the change in Early Treatment Diabetic Retinopathy Score (ETDRS) letters from baseline at 12 months. Secondary outcomes included improvement in retinal thickness from baseline, number of anti-VEGF injections and frequency of adverse events. Outcomes were examined at 12, and 24 months. Certainty of evidence was assessed utilizing GRADE (Grading of Recommendations Assessments, Development and Evaluations) guidelines.

Results:
22 studies including 8 randomized controlled trials, 7 prospective studies, and 7 retrospective studies were included. At 12 months, there was no significant difference in visual acuity when comparing T&E to fixed dosing (mean difference (MD) 0.72 letters, 95% CI -0.73-2.17, moderate evidence) or to PRN dosing (MD -0.89 letters, 95% CI -1.98-0.21, very low evidence). Similarly, at 24-months, there was no significant difference in visual acuity when comparing T&E to fixed (MD 0.09 letters, 95% CI -1.57-1.74, moderate evidence) or to PRN dosing (MD -1.26 letters, 95% CI -2.64-0.13, very low certainty evidence). No significant difference was found in central retinal thickness (CRT) between T&E and fixed regimens at 12-months (MD 12.24, 95% CI -31.62-56.1, low evidence), or at 24-months (MD -10.65, 95% CI -27.93-7.02, low evidence). There was no significant difference in CRT between T&E and PRN regimens at 12-months (9.08 µm, 95% CI -12.94-31.09, very low evidence). Similarly, no significant difference was found between T&E and fixed regimens in central subfoveal thickness at 12-months (MD 0.04, 95% CI -9.62-9.54, moderate evidence). No significant difference existed in injection frequency between T&E and fixed regimens at 12-months (MD -0.36, 95% CI -2.66-1.93, very low evidence). PRN regimens delivered fewer injections compared to T&E regimens at 12 months (MD 2.33, 95% CI 1.19-3.46, very low evidence).

Conclusion:
This review provides a comprehensive assessment of the different treatment algorithms to help guide clinicians and other key stakeholders, including patients and payers, in terms of treatment decisions for management of CI-DME. Our analysis suggests that T&E regimens are an effective dosing strategy that is similar to fixed and PRN with regards to functional and anatomic outcomes at both 12 and 24 months. Additional head-to-head trials, comparing T&E versus fixed and PRN

dosing are needed to provide visual and anatomic outcome data beyond year 2.

IRB APPROVAL No - exempt

Figure 1. PRISMA Flow Diagram

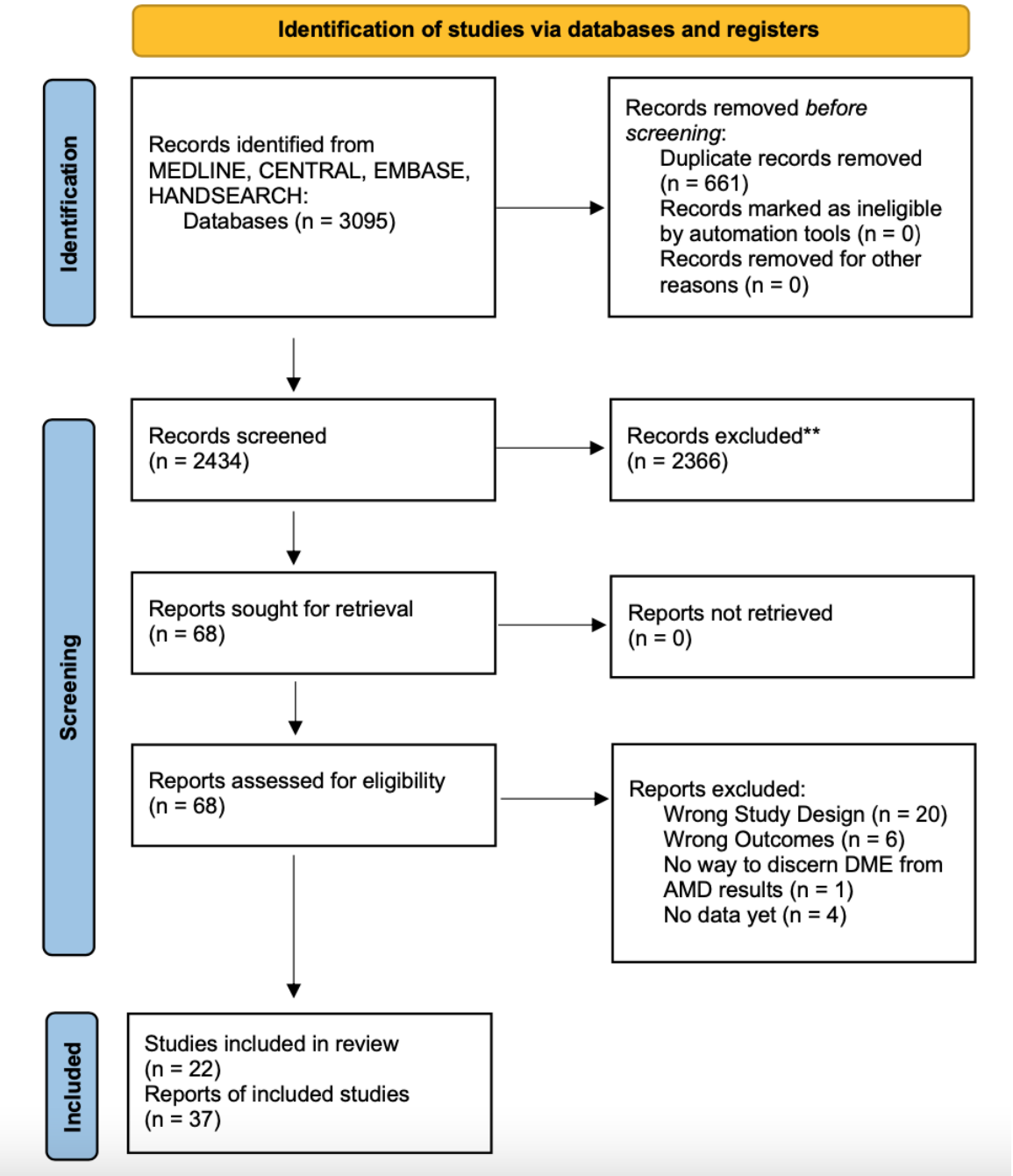


Figure 1. PRISMA Flow Diagram

Table 1. Summary of eligible studies with treat-and-extend (T&E) injection protocol.

#	Study	Date	Study Location	Study Design	Interventions	Drug	Number of eyes (baseline)	Follow-up (months)	Baseline Age	Female (%)
1	RETAIN Prunte et al[42]	2016	International Multicenter	RCT (Year 1,2)	T&E vs PRN	Ranibizumab	T&E n = 249; PRN n = 123	12, 24	63.72	140 (37.6)
2	*TREX-DME* Payne et al[41]	2017	United States	RCT (Year 1)	T&E vs Fixed	Ranibizumab	T&E n = 120; Fixed n = 30	12	59.46	72 (48.0)
	TREX-DME Payne et al[39]	2019	United States	RCT (Year 2)	T&E vs Fixed		T&E n = 120; Fixed n = 30	24		
	TREX-DME Payne et al[40]	2021	United States	RCT (Year 3)	T&E vs Fixed		PRN n = 150	36		
3	Eichenbaum et al[20]	2018	United States	RCT (Year 1, 2)	T&E vs Fixed	Ranibizumab	T&E n = 10; Fixed n = 10	12, 24	62.45	8 (40)
4	Ehlers et al1[19]	2019	United States	RCT (Year 1)	T&E vs Fixed	Ranibizumab	T&E n = 12; Fixed n = 15	12	63.08	16 (59.26)
5	EVADE Giust et al[25]	2018	United States	RCT (Year 1)	T&E vs Fixed	Aflibercept	T&E n = 25; Fixed n = 25	12	NA	NA
6	VIOLET Bayer[8]	2020	International Multicenter	RCT (Year 1, 2)	T&E vs Fixed vs PRN	Aflibercept	T&E n = 154; Fixed n = 155; PRN n = 154	12, 24	64.83	178 (38.44)
7	YOSEMITE Roche[10]	2021	International Multicenter	RCT (Year 1)	T&E vs Fixed	Faricimab Aflibercept	T&E Far = 313; Fixed Far = 313; Fixed Afl n = 311	12	62.20	378 (40.21)
8	RHINE Roche[11]	2021	International Multicenter	RCT (Year 1)	T&E vs Fixed	Faricimab Aflibercept	T&E Far = 319; Fixed Far = 317; Fixed Afl n = 315	12	62.13	372 (39.12)
9	Verma et al[56]	2016	Australia	Prospective (Year 1)	T&E	Aflibercept	T&E n = 24	12	NA	NA
10	JADE Chen et al[5]	2019	Taiwan	Prospective (Year 1)	T&E	Aflibercept	T&E n = 45	12	NA	NA
11	VIBIM Pak et al[38]	2020	Korea	Prospective (Year 1)	T&E	Aflibercept	T&E n = 48	12	59.4	23 (47.92)
	VIBIM Kim et al[31]	2020	Korea	Prospective (Year 2)	T&E		T&E n = 48	24		
12	Mieno et al[34]	2020	Japan	Prospective (Year 1)	T&E	Aflibercept	T&E n = 30	12	NA	20 (66.67)
13	Curry et al[14]	2020	Australia	Prospective (Year 1)	T&E	Aflibercept	T&E n = 26	12, 24	67.4	10 (38.46)
14	TADI Tiosano et al[53]	2021	Israel	Prospective (Year 1)	T&E	Aflibercept	T&E n = 48	12	62	22 (45.83)
15	Hirano et al[29]	2021	Japan	Prospective (Year 2)	T&E	Aflibercept	T&E n = 40	24	66	15 (22.72)
16	Ebneter et al[18]	2016	Switzerland	Retrospective (Year 1)	T&E vs PRN	Ranibizumab	T&E n = 22; PRN n = 24	12	63.30	13 (28.26)
17	Tyagi et al[55]	2016	United Kingdom	Retrospective (Year 1)	T&E	Aflibercept	T&E n = 21	12	70	NA
18	El-Assal et al[21]	2017	United Kingdom	Retrospective (Year 1)	T&E	Aflibercept	T&E n = 57	12	65.2	NA
19	Tsapardoni et al[54]	2019	Greece	Retrospective (Year 1, 2)	T&E	Aflibercept	T&E n = 30	12, 24	68.64	8 (26.67)
20	Chujo et al[6]	2018	Japan	Retrospective (Year 1,2)	T&E	Ranibizumab Aflibercept	T&E Ran = 14; T&E Afl n = 13	12, 24	68.40	NA
21	Sugimoto et al[51]	2017	Japan	Retrospective (Year 2)	T&E	Bevacizumab	T&E n = 42	24	55.4	1 (12.5)
22	Sarici et al[45]	2020	Turkey	Retrospective (Year 1)	T&E vs PRN	NA	T&E n = 44; PRN n = 66	12	NA	NA

RCT, randomized controlled trial; PRN, pro re nata; T&E, Treat and Extend; NA, not available

Table 1. Summary of eligible studies with T&E injection protocol