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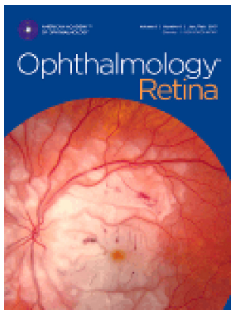

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One-year anti-VEGF therapy outcomes in diabetic macular edema based on treatment intensity: Data from the FRB! registry

Hemal Mehta[1,2], Pierre-Henry Gabrielle[1,3], Yohei Hashimoto[1], Getiye Dejenu Kibret[1], Jennifer Arnold[4], Tremeur Guillaumie[5], Wajiha Jurdi Kheir[6], Gerhard Kok[7], Stela Vujosevic[8,9], Louise O'Toole[10], Els Mangelschots[11], Nandor Jaross[12], Lala Ceklic[13], Vincent Daien[1,14], Francesco Viola[15,16], David Squirrell[17], Francisco Javier Lavid[18], Catherine Creuzot-Garcher[3], Daniel Barthelmes[1,19], Mark Gillies[1].

for the Fight Retinal Blindness! Study Group

[1] The University of Sydney, Sydney Medical School, Discipline of Ophthalmology, Save Sight Institute, New South Wales, Australia

[2] Department of Ophthalmology, Royal Free London NHS Foundation Trust, London, United Kingdom

[3] Department of Ophthalmology, Dijon University Hospital, Dijon, France Eye Clinic

[4] Marsden Eye Specialists, Sydney, New South Wales, Australia

[5] Department of Ophthalmology, Saint Brieuc Hospital, 22000 Saint Brieuc, France

[6] Department of Ophthalmology, American University of Beirut Medical Center, Beirut, Lebanon

[7] Dr. Gerhard Kok Inc. (private ophthalmology practice), Pretoria, South Africa

[8] Department of Biomedical, Surgical and Dental Sciences University of Milan, Milan, Italy.

[9] Eye Clinic IRCCS MultiMedica, Milan, Italy

[10] Mater Private Network, Dublin & University College Dublin, Ireland

[11] Oogartsenpraktijk Alken and Jessa Ziekenhuis Hasselt, Belgium

[12] Australian Eye Specialists (Wyndham), Werribee, Victoria, Australia

[13] University of Vitez, Travnik, Bosnia and Herzegovina

[14] Department of Ophthalmology, Gui de Chauliac Hospital, 80 Avenue Augustin Fliche, 34000, Montpellier, France.

[15] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[16] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

[17] Auckland District Health Board, Auckland, New Zealand.

[18] Department of Ophthalmology, Hospital Punta Europa, Algeciras, Cádiz, Spain.

[19] Department of Ophthalmology, University Hospital Zurich and University of Zurich, Zurich, Switzerland.

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Running head: Anti-VEGF therapy outcomes in DME based on treatment intensity

Corresponding Author/Address for Reprints:

Pierre-Henry Gabrielle, MD, PhD, FEBO

Dijon University Hospital Ophthalmology Department, 14 Rue Paul Gaffarel, 21000, DIJON, France

Phone: 03 80 29 37 56

Fax: 03 80 29 35 89

Email: phgabrielle@gmail.com

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Keywords: Diabetic macular edema, anti-VEGF, VEGF inhibitor, treatment pattern, proactive, treat-and-extend, fixed, reactive regimen, Pro-Re-Nata, real-world evidence, registry.

This article contains additional online-only material.

The following should appear online-only: Figures S1, S2 and Table S4.

Abstract (word count = 233)

Purpose: To compare one-year outcomes of eyes with diabetic macular edema (DME) treated in routine clinical practice based on the proportion of visits where intravitreal vascular endothelial growth factor (VEGF) inhibitor injections were delivered.

Design: Cohort study

Participants: There were 2288 treatment-naïve eyes with DME starting intravitreal VEGF inhibitor therapy from 31 October 2015 to 31 October 2021 from the Fight Retinal Blindness! international outcomes registry.

Methods: Eyes were grouped according to the proportion of visits at which an injection was received, Group A with less than the median of 67% (n=1172) versus Group B with greater than the median (n=1116).

Main Outcome Measure: Mean visual acuity (VA) change after 12 months of treatment.

Results: The mean (95% confidence interval [CI]) VA change after 12 months of treatment was 3.6 (2.8, 4.4) letters for eyes in Group A versus 5.2 (4.4, 5.9) letters for eyes in Group B (p=0.005). The mean (95% CI) central subfield thickness (CST) change was -69 (-76, -61) µm and -85 (-92, -78) µm for eyes in Group A versus Group B, respectively (p=0.002). A moderate positive correlation was observed between the number of injections received over 12 months of treatment and the change in VA (p<0.001). Additionally, eyes that received more injections had a moderately greater CST reduction.

Conclusions: This registry analysis found that overall VA and anatomic outcomes tended to be better in DME eyes treated at a greater proportion of visits in the first year of intravitreal VEGF inhibitor therapy.

Introduction

Fixed interval regimens of monthly or bimonthly intravitreal VEGF inhibitors for DME have been associated with excellent visual outcomes in randomized controlled trials.[1, 2] The challenge of accommodating so many visits, given patients have other health appointments and work commitments, is likely one of the reasons clinical trial outcomes have not been replicated routine clinical care.[3]

Individualized regimens for the treatment of DME have evolved, mainly *pro re nata* (PRN), wherein patients are monitored regularly and treated only when DME is active, or treat-and-extend (T&E), in which the interval between ongoing treatments is extended until the disease reactivates. The Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol I trial reported that the visual improvements observed at year one using PRN dosing for DME were maintained through 5 years with gradually decreasing injection numbers.[4] The main disadvantage with PRN dosing is that whilst the number of injections is reduced it requires frequent visits to monitor disease activity.[5]

Clinical trials of individualized T&E dosing for DME reported that long-term visual and anatomical outcomes were similar to fixed or PRN dosing with significantly fewer visits but more injections.[6-9] The individualized T&E approach has been shown to be effective in neovascular age-related macular degeneration (nAMD).[10, 11] Whether it has benefits in the management of DME in routine clinical practice has yet to be established. Physicians expect to

continue treating eyes with nAMD indefinitely to maintain vision, while we can expect most eyes with DME to progressively reduce and possibly discontinue treatment within three to five years of commencement.[12-14] A T&E regimen producing good visual acuity outcomes with reduced visits in routine clinical practice might be useful in the initial active phase of DME.

This study aimed to compare the one-year treatment outcomes of those eyes with DME treated with VEGF inhibitor injections in routine clinical practice based on the proportion of visits at which treatment was received using data from the prospectively designed Fight Retinal Blindness! (FRB!) registry.

Methods

Design and Setting

The FRB! Registry is a web-based platform for tracking treatment outcomes that uniquely ensures data are 100% complete and in range due to its collection of a minimum essential outcomes set with mandatory fields.[15,16] All patients gave their informed consent. Participants in this analysis came from Australia, France, Spain, New Zealand, United Kingdom, Italy, Switzerland, Bosnia and Herzegovina, Belgium, Lebanon, South Africa and Ireland. Ethics approvals in Australia was obtained from the Sydney Local Health District HREC for public hospitals and the ethics committee of the Royal Australian and New Zealand College of Ophthalmologists for private sites. The international centers obtained approvals from their own relevant local ethics and data protection committees. The data were de-identified at the time of submission before analysis. The study adhered to the tenets of the Declaration of Helsinki and followed the strengthening the reporting of observational studies in epidemiology (STROBE) statements for reporting observational studies.[17]

Data Sources and Measurements

The Fight Retinal Blindness! Registry has a module that collects data from eyes being treated for DME.[19,20] One or both eyes from the same patient were considered for the present analysis. Data were obtained from each clinical visit, including the number of letters read on a logMAR visual acuity (VA) chart (best of uncorrected, corrected or pinhole), type of treatment given, the central subfield thickness (CST [µm]) measured using spectral-domain optical coherence tomography (OCT). Demographic characteristics, duration and types of diabetes, severity grading of diabetic retinopathy (DR) and previous treatments received were recorded at the

baseline visit. Treatment decisions, including type of drug and injection frequency were collected over the follow-up period.

Patient Selection and Groups

All eligible eyes that started treatment for DME with either aflibercept (2mg Eylea, Regeneron Inc/Bayer), bevacizumab (1.25mg Avastin, Genentech Inc/Roche) or ranibizumab (0.5mg Lucentis, Genentech Inc/Novartis) from 31 October 2015 to 31 October 2021 were considered for the study, thereby allowing the possibility of having at least 12 months of follow-up after the start of treatment. Eligible patients must have had at least three visits to establish sufficient ongoing follow-up. The one-year endpoint was the closest visit to 365 ± 90 days. Eyes that completed at least 12 months of visits were defined as "completers" and eyes that did not complete 12 months of observations were "non-completers." Eyes were divided into two groups based on the median number of injections per visit (median = 67%). Group A had fewer than the median number of injections per visit while Group B had more than the median.

Main and Secondary Outcomes

The main outcome was the mean change in VA from baseline at 12 months between eyes in Group A and B. Secondary outcomes included the mean change in CST, number of visits and injections over 12 months of treatment, VA and CST. Age, type of drug, visual acuity and CST at presentation and number of injections per visit in the 12 months follow-up were considered as explanatory variables.

Statistical Analysis

Descriptive statistics such as mean with standard deviation (SD), median with first and third quartiles (Q1, Q3) and percentages were calculated for baseline characteristics and outcomes, stratifying by proportion of injections per visit. The unit of analysis for visual outcomes was eyes. As a result of the possible variation in regimen and treatment follow-up times between individual eyes of a patient; eyes of the same patient could have different treatment pattern and outcomes. Crude visual outcomes at 12 months were calculated using the last observation carried forward method for non-completers. T-tests, Wilcoxon rank sum tests, chi-square tests and Fisher's exact tests were used as appropriate to compare baseline characteristics and visual outcomes between eyes in Group A and B. Partial correlation with Kendall's method was used to see the associations between baseline features, injection frequency and outcome measurements. A multivariable linear mixed effects model was performed in lme4 package to see the effects of baseline characteristics and injection frequencies on VA change, considering within clinicians' and within patient differences as random effects.[18] Variance Inflation Factor (VIF) was used to detect multicollinearity between variables in the multivariable model using the VIF function in R. All analyses were conducted using R software version 4.2.1.

Results

Study participants

A total of 2288 treatment naïve DME eyes of 1572 patients from 1 October 2015 and 31 October 2021 were identified. The flowchart showing the number of eyes at each selection criterion is shown in Figure S1 (available at https://www.ophthalmologyretina.org/). The mean (SD) age was 63.8 (12) years and 39% were female. The large majority (88%) of patients had type 2 diabetes and the mean (SD) duration of diabetes was 16 (10) years. The mean (SD) VA and CST at baseline were 64.6 (17.6) letters and 404 (121) µm, respectively. There were 81% of eyes with non-proliferative diabetic retinopathy (NDPR) at baseline (Table 1).

Outcomes according to dosing groups

Outcomes were compared with the proportion of injections delivered per visit < median (Group A n=1172 eyes) versus > median (Group B n=1116 eyes) over the first 12 months of treatment. Non-completers, whose data were analyzed using the last observation carried forward, accounted for 20% (n = 236) of eyes in Group A and 25% (n = 275) of eyes in Group B. Group B had moderately greater visual improvement (mean [95% CI] change in VA, 5.2 [4.4, 5.9] letters *versus* 3.6 [2.8, 4.4] letters for Group A, p = 0.005) and moderately better reduction in macular thickness (mean [95% CI] in CST for Group B -85 [-92, -78] µm *versus* -69 [-76, -61] µm for Group A, p = 0.002 after 12 months. Unsurprisingly, Group B received significantly more injections (median (Q1, Q3), 7 [5, 9], *versus* 4 [3, 6] for Group A, p < 0.001) with a lower interval from the last injection to the final 12-month visit (mean (SD) 24 [58] *versus* 125 [130] days for Group A, p <0.001) and had a lower median (Q1, Q3) number of visits (8 [5, 11] *versus* 9 [7, 13] for Group

A, $p < 0.001$ (Table 2). Figure S2 reports the relationship between VA and CST and the proportion of injection per visit (available at https://www.ophthalmologyretina.org/). Table 3 reports the results of the adjusted mean change in VA at 12 months by type of dosing, baseline age, initial type of VEGF inhibitors, baseline VA and CST using a multivariable linear mixed effects regression model. Eyes of younger patients (beta coefficient β [95% CI] = -0.09 [-0.13, -0.04], $p < 0.001$), with worse baseline visual acuity (β = -0.37 [-0.40, -0.33], $p < 0.001$) and receiving more than the median number of VEGF inhibitor injections per visit (β (95% CI) = 1.24 [0.20, 2.28], p = 0.019) had significantly better visual gain at 12 months. There was no significant difference in visual outcomes between types of VEGF inhibitor (Table 3).

Outcomes according to injection frequency

Visual and anatomical outcomes were analyzed by baseline features and number of injections over 12 months. There was a negative correlation between VA at first treatment and change in mean visual acuity at 12 months ($\tau(19.7) = -0.32$, $p<0.001$), indicating greater VA changes for eyes with lower VA at baseline (Figure 3). A positive correlation was observed between the number of injections received over 12 months and the change in visual acuity ($\tau(4.4) = 0.07$, $p<0.001$) (Figure 4). Eyes with thicker CST (μm) at baseline tended to receive more injections over 12 months (Figure 5). After controlling for baseline clinical characteristics, eyes with DME receiving greater number of injections over 12 months had moderately greater mean VA improvement (Kendall's partial correlation coefficient $\tau = 0.04$, $p = 0.010$) and moderately greater reduction in CST (Kendall's partial correlation coefficient $\tau = -0.09$, $p < 0.001$) at 12 months (Table S4, available at https://www.ophthalmologyretina.org/).

Discussion

This analysis of 12-month outcomes of eyes with DME treated with intravitreal VEGF inhibitors in routine clinical practice identified moderate visual acuity gains regardless of the proportion of visits where intravitreal therapy was delivered. There was a small visual acuity benefit in favor of the more intensively treated group which, by definition, received more injections at fewer visits. These results indicate that for DME a proactive T&E protocol yields superior results with fewer visits compared with less intensive treatment regimens in the first year of treatment.

Eyes with worse baseline vision received more intravitreal injections over the initial 12 months with greater potential for visual acuity gain (Figure S2, available at https://www.ophthalmologyretina.org/). This is consistent with a large study of 28658 eyes with DME treated in routine clinical practice in the USA.[19] Similarly, eyes with greater CST at baseline, required more intravitreal injections over the initial 12 months with greater potential for reduction in CST. This suggests that initiating treatment earlier may reduce the overall treatment burden. There is likely to be a balance between initiating treatment too early as evidenced by the results of DRCRnet Protocol V and delaying treatment often as a result of local reimbursement policies.[20] [21]

Eyes of younger patients had significantly better visual acuity gains at 12 months. Older patients may have age-related changes such as epiretinal membranes or macular degeneration that potentially limit visual gains. This highlights the importance of comparative groups in DME clinical trials being well matched for age at baseline.

The main advantage of proactive T&E regimens over reactive PRN approaches relates to reduced clinic visits. This can potentially reduce the appointment burden for patients and provides certainty to patients that treatment will be delivered at most visits. This certainty can also help in the planning of intravitreal therapy delivery services. The main disadvantage of proactive T&E regimens relates to the marginally higher number of intravitreal injections required, although this appears to translate to improved visual outcomes in the first year of therapy in routine clinical practice. No difference in the rate of endophthalmitis was observed between the treatment groups although the study was not powered to identify potentially significant rates of this rare adverse event.[22]

The median proportion of visits where an injection was delivered was 67% for the entire cohort. Before October 2018, 45% of eyes were treated with intravitreal VEGF inhibitor therapy at greater than two-thirds of visits but after October 2018 this increased to 54%. This suggests a trend towards more proactive treatment regimens over the duration of the study, perhaps as the T&E evidence base in DME built. However, if home OCT technology improves then it would become possible for disease activity to be assessed away from the clinic supporting PRN treatment approaches.[23]

Figures 2 and 3 demonstrate the considerable heterogeneity in treatment needs of eyes with DME. This supports the use of PRN or T&E approaches over fixed interval dosing to personalize treatment. In patients in whom the priority is to reduce clinic visits, there is an argument to employ a T&E approach until disease stability with a 12 to 16 week treatment interval has been achieved and then transition to a PRN approach, likely from year 3 to 5 of treatment.

283 There was a greater number of eyes treated with panretinal laser photocoagulation (PRP) in
284 Group A. These eyes received less consistent VEGF inhibitor therapy which could be associated
285 with a greater risk of proliferative diabetic retinopathy inferring from results of DRCRnet
286 Protocol S and CLARITY.[24,25] Another consideration is that visits associated with delivery of PRP
287 would reduce the proportion of visits dedicated to intravitreal anti-VEGF therapy.
288 The higher use of supplementary intravitreal steroid in Group A may have resulted in fewer
289 anti-VEGF injections and more visits without injections to monitor and treat raised intraocular
290 pressure and cataract progression.[26] However, baseline characteristics between groups were
291 well matched for age, sex and diabetes duration (Table 1).
292 Some issues affect the interpretation of the results. This retrospective analysis of data from the
293 prospectively designed FRB! registry does not have the same internal validity as a randomized
294 controlled trial. However, the broad populations included in routine clinical practice helps
295 support generalizability of results. Injections received at the last observation were included in
296 the analysis, which may have inflated the median number of injections in Group B than Group
297 A. However, censoring or deleting data from the most recent visit in the group would have led
298 to excluding most eyes in Group B from the entire analysis because eyes treated with T&E
299 dosing get treated at every visit with almost 80% of eyes in Group B treated at the last
300 observation in our cohort. High dropout rates are a feature and a limitation of observational
301 studies. There was no significant difference between the mean VA change in the completers
302 and non-completers for Group A, Group B or overall eyes. We present only 12 months
303 outcomes, the differences we observed may not have endured with longer follow-up. A

strength of the analysis is the quality of the FRB! outcomes data due to the use of mandatory fields to track a structured minimum dataset.[15]

Patients with mild DME may have been treated less intensively but still had a good outcome because they responded quickly, whereas other patients with more severe disease may have been treated more intensively but still had inferior outcomes. An analysis based on the general treatment intensity of individual practitioners might produce a clearer picture by avoiding this potential source of bias.

Further research is warranted to assess variability in delivery of intravitreal VEGF therapy between and within countries. The impact of local reimbursement arrangements on DME outcomes between countries likely affects outcomes. Understanding the differences of individual or clinic practice patterns within the same country can also provide a valuable opportunity for benchmarking and improving patient outcomes. In the published clinical trials of T&E in DME, there has been considerable variability in the actual regimen employed between studies. For example, in the recently published LADAMO clinical trial, no loading phase was required and clinicians had the ability to extend treatment intervals as soon as the DME was stable.[27] Comparative work to establish the most effective T&E regimen to use in routine clinical practice for DME is required.

In conclusion, visual and anatomic outcomes were modestly better in eyes treated with an intensive treatment regimen with intravitreal VEGF inhibitors in the first year of treatment for DME. Treat-and-extend approaches offer a valid alternative to PRN regimens, particularly in the early years of DME treatment when the disease is more active.

Acknowledgments

Fight Retinal Blindness! Investigators:

Name	Country	Practice
Admir Miri	France	CH Saint Brieuc
Adrian Fung	Australia	Retina Associates
Alejandro Higueras	Spain	Hospital Can Misses
Alessandro Invernizzi	Italy	Luigi Sacco Hospital - University of Milan
Alex Hamilton	Australia	Sydney Eye Surgeons (Miranda)
Amy Cohn	Australia	Specialist Eye Group
Ann Vanderschueren	Belgium	Oogartsenpraktijk Alken
Benjamin Wolff	France	Maison rouge Ophthalmologic center
Bougamha Walid	France	CHU de Nice Pasteur 2
Charles Hennings	United Kingdom	Royal Free London NHS Foundation Trust
Charmaine Chung	Australia	Strathfield Retina Clinic
Chris Hornsby	Australia	C.W.Hornsby Medical
Cinthia Rethati	Spain	FPHAG
Daniel Barthelmes	Switzerland	USZ_AUG
Daniel Velazquez Villoria	Spain	Villoria Clinic
David Squirrell	New Zealand	Auckland District Health Board, Auckland, New Zealand.
Derek Chan	Australia	Marsden Eye Specialists
Elaine Chong	Australia	Hawthorn Eye Clinic

Els Mangelschots	Belgium	Oogartsenpraktijk Alken
Ester Carreño	Spain	Hospital Universitario Fundacion Jimenez Diaz
Florian Baudin	France	CHU de Dijon
Francesco Viola	Italy	Fondazione IRCCS CA'GRANDA - Ospedale Maggiore Policlinico
Francisco Javier Lavid	Spain	Hospital Punta de Europa
Gerhard Kok	South Africa	Montana Private Hospital
Graham Furness	Australia	Insight Eye Clinic
Guillaume Michel	France	Maison rouge Ophthalmologic center
Heather Mack	Australia	Eye Surgery Associates (East Melb)
Helen Steiner	Australia	Dorset Consultant Center
Hemal Mehta	United Kingdom	Royal Free London NHS Foundation Trust
Ian Reddie	Australia	North Queensland Retina
James Acton	South Africa	Dr James Acton
Jane Wells	Australia	Canberra Hospital
Jennifer Arnold	Australia	Marsden Eye Specialists
Joel Suarez	Spain	FPHAG
Jolly Gilhotra	Australia	Adelaide Eye & Retina Centre
Justin Oday	Australia	Victoria Parade Eye Consultants
Lala Ceklic	Bosnia and Herzegovina	ZU Centar za zaštitu vida- Vidar Lala MD
Laura Sararols	Spain	FPHAG

Les Manning	Australia	Les Manning
Li Ping Chow	Australia	Hawthorn Eye Clinic
Louise OToole	Ireland	Mater Private Hospital
Luis Cordoves	Spain	Hospital Universitario de Canarias
Maite Arrazola	Spain	Hospital Universitario Basurto
María Eugenia Tena Sempere	Spain	Hospital San Juan de Dios del Aljarafe
Maria Pilar Navarro	Spain	Hospital Dos de Maig
Mark Gillies	Australia	Eye Associates
Mark Morgan	Australia	New England Eye Centre
Marta Rodriguez Núñez	Spain	Hospital do Meixoeiro
Michel Weber	France	CHU de Nantes
Miguel Castilla Marti	Spain	Hospital del Mar
Miguel de la Fuente	Spain	Hospital Universitario Ramon y Cajal
Monica Asencio Duran	Spain	Hospital Universitario La Paz
Nandor Jaross	Australia	Australian Eye Specialists (Wyndham)
Pablo Catalán Muñoz	Spain	Hospital San Juan de Dios del Aljarafe
Pablo Carnota	Spain	Centro de Ojos de La Coruña
Patrick Lockie	Australia	St John of God Hospital Geelong
Paul Beaumont	Australia	Eye Doctors Mona Vale
Peter Hinchcliffe	Australia	Tamworth Eye Centre
Pierre-Henry Gabrielle	France	CHU de Dijon

Pilar Calvo	Spain	Hospital Universitario Miguel Servet
Rachel Barnes	New Zealand	Retina Specialists
Raj Chalasani	Australia	Retina & Macula Specialists (Miranda)
Richard Barry	Australia	Blink
Robert Chong	Australia	Retina Associates
Roberto Gallego-Pinazo	Spain	Clinica Oftalvist Valencia
Ross Ferrier	Australia	Coastwide Eye Surgery
Samantha Fraser-Bell	Australia	Retina Associates
Sandrine Allieu	France	Clinique Beau Soleil
Sanjeev Wickremasinghe	Australia	Doncaster Eye Center
Sarah Tick	France	CHNO des Quinze-Vingts
Sarah Welch	New Zealand	Auckland Eye
Saturnino Manuel Gismero Moreno	Spain	Hospital Costa del Sol
Simon Nothling	Australia	Retina & Macula Specialists (Miranda)
Sonia Aparicio-Sanchis	Spain	Hospital Universitario de La Princesa
Stela Vujosevic	Italy	University Hospital Maggiore della Carita
Stephanie Young	Australia	Gladesville Eye Specialists
Sue Wan	Australia	Parke Street Specialist Centre
Terence Tan	Australia	Marsden Eye Specialists
Tremeur Guillaumie	France	CH Saint Brieuc
Vincent Daien	France	Montpellier CHU

Wajiha Kheir	Lebanon	AUBMC
Xavier Valldeperas	Spain	Hospital Universitari Germans Trias i Pujol
Zanne Louw	Australia	Eye Wide Bay
Ziad Bashshur	Lebanon	AUBMC

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Figure captions

Figure 3. Mean VA change from baseline at 12 months according to the median number of injections over 12 months. The base of each arrow represents the mean baseline visual acuity and the tip corresponds to the mean final visual acuity.

Figure 4. Relationship between the mean change in visual acuity (letters) from baseline at 12 months and the median number of injections over 12 months. Each individual black data point represents a single eye. The blue line represents the line of best fit and the grey shade is the 95% confidence interval. Figure B is the same plot as Figure A but zoomed in to better see the trend of the best fit line. Pearson's correlation coefficient, r, is reported at the top of plot.

Figure 5. Relationship between the number of injections over 12 months and the central subfield thickness at baseline and mean change from baseline at 12 months. Each individual data point represents a single eye. Baseline data are shown in red and 12-month CST change data are shown in blue. Pearson's correlation coefficient, r, is reported on the plot for each line of best fit.

Table 1. Baseline demographic and clinical characteristics of eyes included in the study

	Overall	Treatments per visit		P[a]
		Group A <67%	Group B >67%	
Eyes, n	2288	1172	1116	
Patients, n	1572	892	795	
Female gender, n (%)	39	39	39	0.90
Age, mean (SD)	63.8 (12)	64.2 (12)	63.3 (11.9)	0.06
Diabetes				
Duration in years, mean (SD)	16 (9.9)	16.8 (9.9)	15.2 (9.9)	<0.001
Diabetes Type, n (%)				
Type 1	256 (11.2)	135 (11.5)	121 (10.8)	0.66
Type 2	2014 (88)	1028 (87.7)	986 (88.4)	0.66
Unknown	18 (0.8)	9 (0.8)	9 (0.8)	-
Diabetic retinopathy grade, n (%)				
Mild NPDR	455 (19.9)	264 (22.5)	191 (17.1)	0.001
Moderate NPDR	810 (35.4)	379 (32.3)	431 (38.6)	0.002
Severe NPDR	586 (25.6)	286 (24.4)	300 (26.9)	0.19
Low-Risk PDR	179 (7.8)	92 (7.8)	87 (7.8)	1.0
High-Risk PDR	126 (5.5)	77 (6.6)	49 (4.4)	0.03
Treated PDR	132 (5.8)	74 (6.3)	58 (5.2)	0.29
Visual acuity, logMAR score letters				
Mean (SD)	64.6 (17.6)	63.9 (18.6)	65.3 (16.4)	0.049
≤ 35 letters, n (%)	193 (8.4)	116 (9.9)	77 (6.9)	0.01
≥ 70 letters, n (%)	1217 (53.2)	620 (52.9)	597 (53.5)	0.80
CST (µm), mean (SD)	404 (121)	398 (122)	411 (119)	0.01
Type of VEGF inhibitors, n (%)				
Bevacizumab	426 (18.6)	129 (11)	297 (26.6)	<0.001
Aflibercept	1247 (54.5)	656 (56)	591 (53)	0.07
Ranibizumab	594 (26)	366 (31.2)	228 (20.4)	<0.001
Unknown	21(0.9)	21(1.8)	0(0)	
Year treatment started, n (%)				
2015-10-31 to 2018-10-31	1425 (62.3)	784 (66.9)	641 (57.4)	<0.001
2018-11-01 to 2021-10-31	794 (34.7)	353 (30.1)	441 (39.5)	<0.001

a- calculated from t-test or Chi-square test

n – Number, SD – Standard Deviation, NPDR – Non-Proliferative Diabetic Retinopathy, PDR – Proliferative Diabetic Retinopathy, VA – Visual Acuity, VEGF – Vascular Endothelial Growth Factor, CST – Central Subfield Thickness, DME – Diabetic Macular Edema

Table 2. Visual and anatomical outcomes at 12 months in eyes that received less than (Group A) or greater than (Group B) the median number of injections per visit

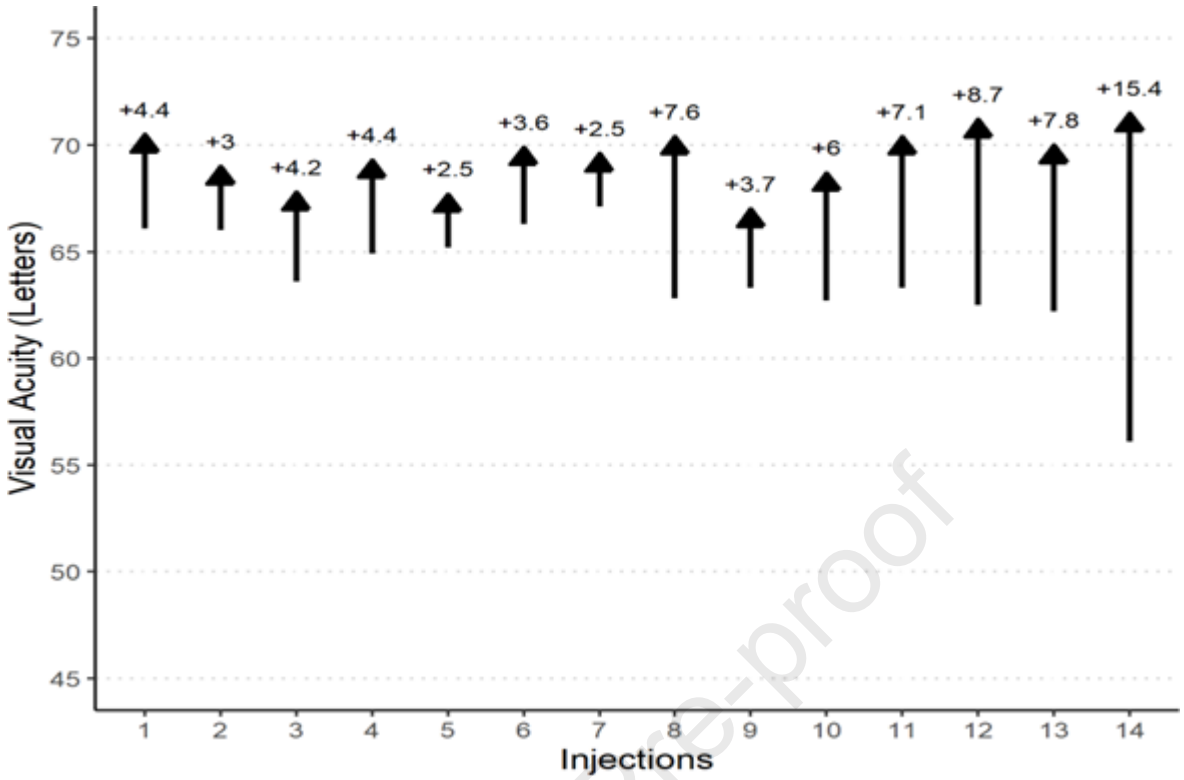
	Treatments per visit		
	Group A <67%	**Group B >67%**	**P**
Eyes, n (%)	1172	1116	
Non-completers, n (%)	236 (20)	275 (25)	
Visual acuity, logMAR score letters			
At first treatment, mean (SD)	63.9 (18.6)	65.3 (16.4)	0.049
Final, mean (SD)	67.5 (18.3)	70.5 (14.2)	<0.001
Final <= 35, n (%)	85 (7.3)	43 (3.9)	<0.001
Final >= 70, n (%)	710 (60.6)	762 (68.3)	<0.001
Change, mean (95% CI)	3.6 (2.8, 4.4)	5.2 (4.4, 5.9)	0.005
VA gain >=10, n (%)	284 (24.2)	319 (28.6)	0.02
VA loss <= -10, n (%)	113 (9.6)	81 (7.3)	0.049
Central subfield thickness, µm			
At first treatment, mean (SD)	398 (122)	411 (119)	0.01
Final, mean (SD)	328 (99)	326 (94)	0.52
Change, mean (95% CI)	-68.5 (-76, -61)	-85 (-92, -78)	0.002
Treatment outcomes			
Number of visits, median (Q1, Q3)	9 (6.8, 13)	8 (5, 11)	<0.001
Number of injections, median (Q1, Q3)	4 (3, 6)	7 (5, 9)	<0.001
Last Interval of injections, days median (Q1, Q3)	40 (28, 70)	48 (33, 77)	<0.001
Interval from last injection to observation end, days median (Q1, Q3)	82 (0, 223)	0 (0, 5.2)	<0.001
Interval from last injection to observation end, days mean (SD)	125 (130)	24 (58)	<0.001
Thermal macular laser, n (%)	31 (2.6)	31 (2.8)	0.95
Subthreshold macular Laser, n (%)	2 (0.2)	1 (0.1)	1.0
Pan retinal laser photocoagulation, n (%)	283 (24.1)	51 (4.6)	<0.001
Triamcinolone, n (%)	18 (1.5)	7 (0.6)	0.06
Fluocinolone implant (Iluvien), n (%)	1 (0.1)	0 (0)	1.0
Dexamethasone implant (Ozurdex), n (%)	153 (13.1)	20 (1.8)	<0.001
Vitrectomy, n (%)	9 (0.8)	3 (0.3)	0.17

n – Number, SD – Standard Deviation, DME – Diabetic Macular Edema, Q1 – first quartile, Q3 – third quartile,

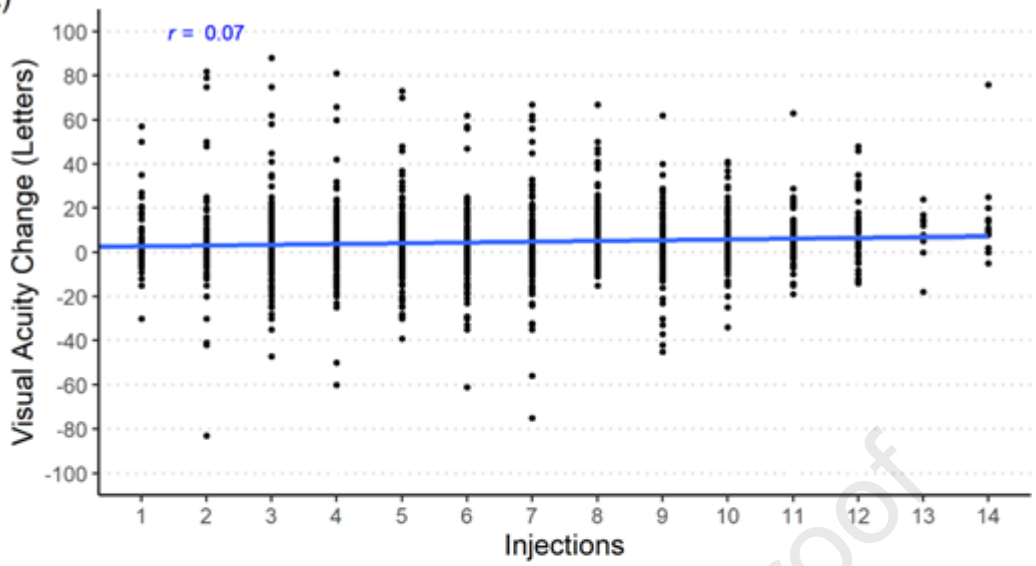
Table 3. Results from multivariate regression model for visual acuity change at 12 months

Variables	β coefficients (95% CI) [a]	P
Treatment dosing		
<67% treatments per visit	Reference	
>67% treatments per visit	1.24 (0.20, 2.28)	0.019*
Baseline age	-0.09 (-0.13, -0.04)	<0.001*
Initial type of VEGF inhibitors		
Bevacizumab	Reference	
Aflibercept	0.38 (-1.28, 2.03)	0.65
Ranibizumab	0.20 (-1.63, 2.03)	0.83
Baseline visual acuity	-0.37 (-0.40, -0.33)	<0.001*
Baseline central subfield thickness	0.0006 (-0.004, 0.005)	0.79

[a] Calculated from multivariate linear mixed-effects regression model adjusting for age, visual acuity, central subfield thickness and type of VEGF inhibitors at baseline (fixed-effects), and clinicians' and within patient differences (random-effects).
*Significant P-values.



A)



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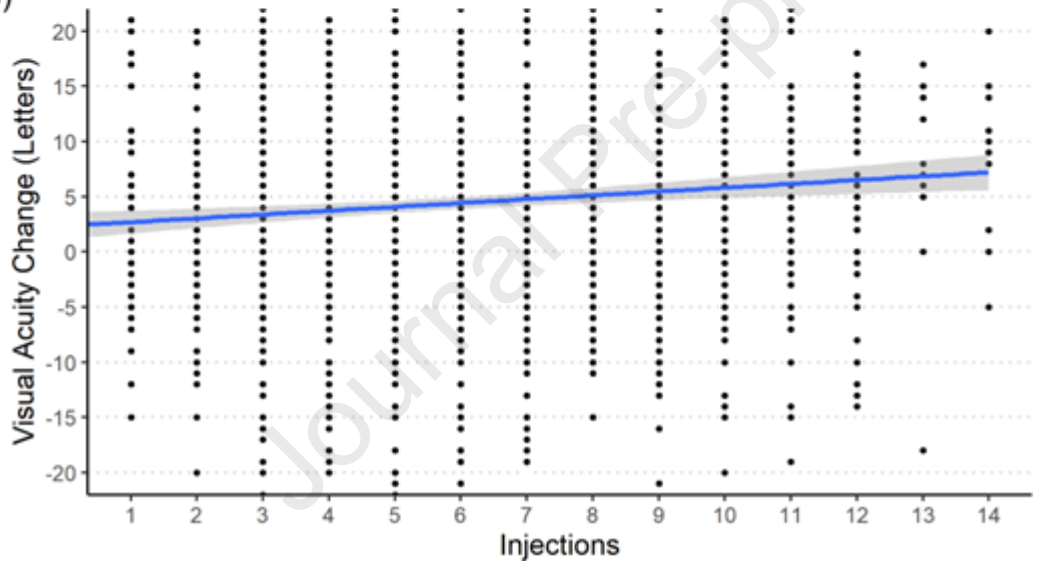

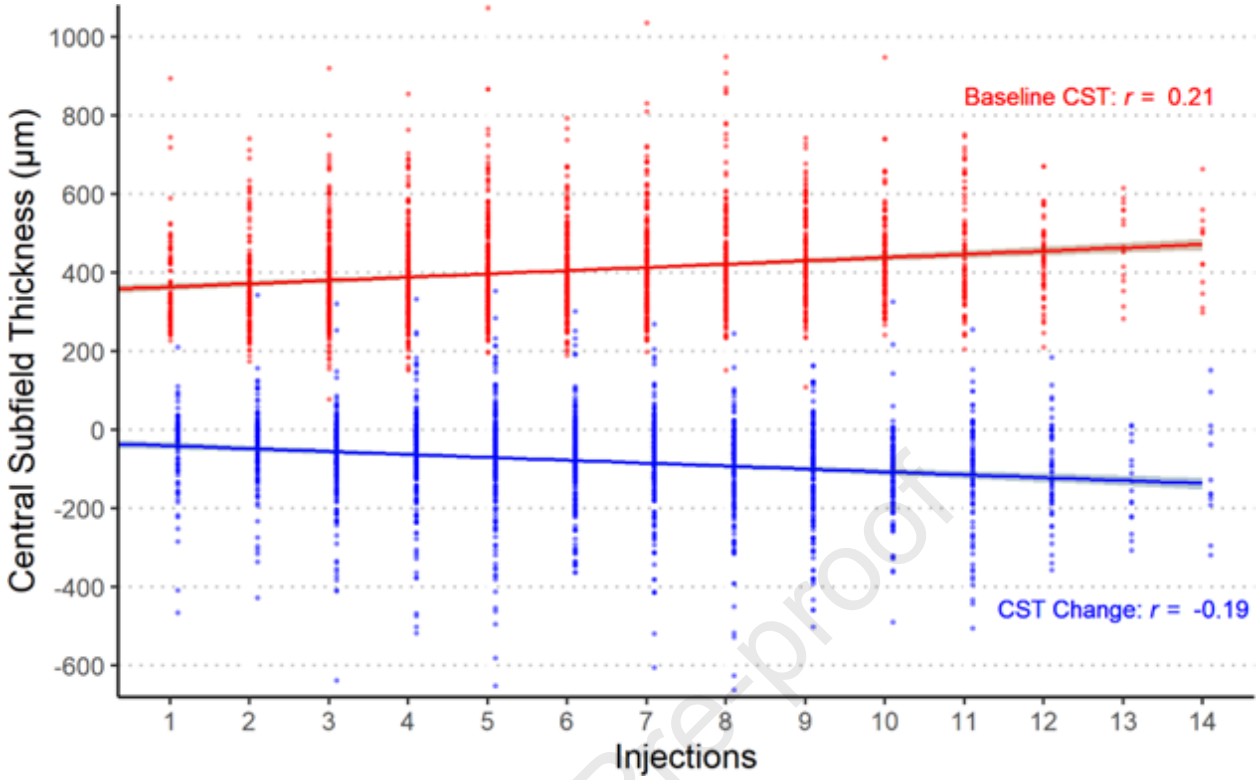

Precis

This analysis of registry data found that patients receiving intravitreal VEGF inhibitors for diabetic macular edema at more than two-thirds of their visits, a measure of their practitioner's treatment intensity, generally had better 12-month visual acuity and anatomic outcomes