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Evolving Treatment Patterns in Diabetic Macular Edema Between 2015 and 2020

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Abstract

Purpose: To explore the recent evolution of diabetic macular edema (DME) treatment practice patterns over 5 years among retina specialists in the United States. **Methods:** This retrospective analysis assessed 306 700 eyes with newly diagnosed DME from the Vestrum Health database between January 2015 and October 2020. The year-over-year and cumulative 5-year distributions of eyes treated with antivascular endothelial growth factor (anti-VEGF) agents, steroids, focal laser, or any combination and those of untreated eyes were calculated. Changes from baseline visual acuity were assessed. **Results:** Yearly treatment patterns changed significantly from 2015 (n = 18056) to 2020 (n = 11042). The proportion of untreated patients declined over time (32.7% vs 27.7%; $P < .001$), the use of anti-VEGF monotherapy increased (43.5% vs 61.8%; $P < .001$), the use of focal laser monotherapy declined (9.7% vs 3.0%; $P < .001$), and the use of steroid monotherapy remained stable (0.9% vs 0.7%; $P = 1.000$). Of eyes that maintained follow-up for 5 years (from 2015 to 2020), 16.3% were untreated while 77.5% were treated with anti-VEGF agents (as monotherapy or combination therapy). Vision gains in treated patients remained approximately stable from 2015 (3.6 letters) to 2020 (3.5 letters). **Conclusions:** From 2015 to 2020, treatment patterns for DME evolved toward greater anti-VEGF monotherapy, stable steroid monotherapy, less laser monotherapy, and fewer untreated eyes.

Keywords

antivascular endothelial growth factor injection, anti-VEGF, intravitreal steroids, focal laser therapy, diabetic macular edema

Introduction

Diabetic macular edema (DME) is the primary cause of visual impairment associated with diabetic retinopathy.[1] With the projected rise in the prevalence of diabetes worldwide, there is a growing need to optimize the management of DME.[2] Understanding historic and current practice patterns for DME by retina specialists can help us better understand the evolving landscape of treatment.

Before the advent of intravitreal therapy, macular focal laser had long been the primary treatment option for DME. The Early Treatment of Diabetic Retinopathy Study (ETDRS) was a National Eye Institute–sponsored, multicenter randomized clinical trial in 1995 whose results showed the benefit of argon laser treatment in eyes with clinically significant DME.[3] The advent of intravitreal therapy in the mid-2000s changed the face of DME management. Pivotal clinical trials helped establish antivascular endothelial growth factor (anti-VEGF) agents as a first-line therapy for DME, showed the efficacy of intravitreal steroid therapy, and provided insight into the relative efficacy of particular anti-VEGF agents for DME.[4–14] Intravitreal therapy has evolved as the standard of care for the treatment of DME.

Few studies have assessed the recent long-term trends of DME management on a large scale.[15,16] Using real-world practice pattern data, we sought to quantify recent shifts in DME practice patterns by US retina specialists.

Methods

Data Collection

A retrospective review of records from January 2015 through October 2021 in the Vestrum Health Retina database was performed. This aggregated, longitudinal database has electronic medical records (EMRs) from a demographically and geographically diverse patient sample, which was obtained from a

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Table 1. Distribution of Diabetic Macular Edema Treatment Between 2015 and 2020.

	Treatment Distribution by Year (%)						
Treatment	2015 (n = 18 056)	2016 (n = 21 416)	2017 (n = 23 818)	2018 (n = 24 711)	2019 (n = 23 856)	2020 (n = 11 042)	2015–2020 (n = 12 918)
Untreated	32.7	31.8	30.5	30.2	31.1	27.7	16.3
Anti-VEGF	43.5	47.2	51.1	54.5	57.1	61.8	48.0
Anti-VEGF + steroid	2.6	3.0	2.8	2.8	2.5	3.0	7.5
Anti-VEGF + laser	9.7	8.1	7.3	5.7	4.2	3.5	18.2
Anti-VEGF + steroid + laser	0.8	0.7	0.6	0.4	0.3	0.1	3.8
Steroid	0.9	1.0	0.8	0.7	0.6	1.0	0.6
Steroid + laser	0.2	0.2	0.2	0.2	0.2	0.1	0.2
Laser	9.7	8.0	6.7	5.5	4.0	3.0	5.4
Anti-VEGF (total)	56.5	59.0	61.8	63.4	64.1	68.4	77.5
Anti-VEGF distribution							
Bevacizumab	47.0	48.0	46.0	45.0	44.0	36.0	35.0
Ranibizumab	15.0	12.0	16.0	24.0	24.0	19.0	17.0
Aflibercept	38.0	40.0	38.0	31.0	32.0	45.0	48.0

Abbreviations: n, number of eyes; VEGF, vascular endothelial growth factor.

panel of US retina specialists (Vestrum Health, LLC, Naperville, IL). All patient information was de-identified in accordance with the regulations of the US Health Insurance Portability and Accountability Act of 1996. The names of the treating physicians and practices were removed from the data. This project was considered exempt from institutional review board review because the research involved the collection of existing de-identified data.

Study Design

Eyes with newly diagnosed DME during the study period were included for analysis. Eyes with less than 1 year of follow-up were excluded, as were eyes with pathology other than DME that might have been treated with intravitreal or macular focal laser therapy (eg, age-related macular degeneration, retinal vein occlusion, myopic choroidal neovascularization). The cumulative 5-year analysis included only the subset of eyes with 5 or more years of follow-up data from 2015 through 2021.

Baseline characteristics recorded included age, sex, and Snellen visual acuity (VA). The year-over-year and cumulative 5-year distributions of eyes treated with anti-VEGF, steroids, focal laser, or combination therapy (defined as any combination of the above used at any time) were recorded along with those of untreated eyes. The mean changes from baseline VA were assessed.

Statistical Analysis

All analyses were performed per individual eye. For bilaterally treated patients, each patient eye was treated independently and the results were recorded in the appropriate cohort.

Baseline characteristics were summarized with descriptive statistics. The mean values (±SD) for patient demographics, number of injections, and baseline and final VA were calculated. Visual acuity outcomes were compared with the baseline VA. This analysis was also performed after the eyes were stratified by baseline VA within each cohort. An equality of proportions analysis was performed using Stata software (version 17.0, StataCorp LLC); the results were used to compare year-to-year and cumulative averages of different therapies. The level of significance was set at $P < .05$.

Results

Between January 2015 and October 2021, 306 700 eyes with newly diagnosed DME were identified. After exclusion criteria, 122 899 eyes were included in the study.

Treatment patterns changed significantly from 2015 (n = 18 056) to 2020 (n = 11 042) (Table 1). The proportion of untreated patients declined (32.7% vs 27.7%; $P < .001$), the use of anti-VEGF monotherapy increased (43.5% vs 61.8%; $P < .001$), the use of focal laser monotherapy declined (9.7% vs 3.0%; $P < .001$), and steroid monotherapy remained stable (0.9% vs 0.7%; $P = 1.000$). There were shifts in the use of combination therapy between 2015 and 2020 (Table 1). There was a decline in combination therapy with anti-VEGF + laser therapy (9.7% vs 3.5%; $P < .001$) and anti-VEGF + steroid + laser therapy (0.8% vs 0.1%; $P < .001$), consistent with a trend toward decreasing focal laser use over time. VA gains in treated patients remained approximately stable from 2015 (3.6 letters) to 2020 (3.5 letters) (Table 2).

Of eyes that maintained follow-up for 5 years (from 2015 to 2020; 12 918 eyes), 16.3% were untreated (Table 1). Anti-VEGF therapy was used in 77% of eyes, as monotherapy in 48% of eyes or as combination therapy in 29.5% of eyes (anti-VEGF therapy + laser, 18.2%; anti-VEGF therapy + steroid, 7.5%; anti-VEGF therapy + steroid + laser 3.8%). The mean number of total anti-VEGF injections per eye over those 5 years was 15.4, with a mean of 4.0 injections in year 1, 2.8 in year 2,

Table 2. Visual Acuity in Treated and Untreated Eyes Between 2015 and 2020.

	Distribution of Average Visual Acuity Gains or Losses (ETDRS Letters)						
Treatment	2015	2016	2017	2018	2019	2020	2015–2020
Untreated	0.4	−0.3	−0.5	−0.6	−0.4	−0.7	−3.1
Anti-VEGF	3.9	3.7	3.3	3.0	3.4	3.4	−0.6
Anti-VEGF + steroid	2.4	4.2	2.9	2.8	3.2	3.8	−3.4
Anti-VEGF + laser	2.2	2.4	1.9	1.5	1.4	1.8	−2.5
Anti-VEGF + steroid + laser	5.7	0.0	2.2	−0.8	2.5	−4.1	−2.2
Steroid	3.8	5.6	2.4	2.5	−0.3	2.3	−8.6
Steroid + laser	−1.9	7.8	4.1	0.4	−4.0	0.9	−4.6
Laser	−1.0	−0.9	−1.0	−1.6	−0.8	−2.1	−3.8
Anti-VEGF (total)	3.6	3.5	3.1	2.8	3.2	3.4	−1.5
Steroid (total)	3.1	4.0	2.8	2.3	2.4	3.3	−3.2
All treated	3.6	3.6	3.2	2.9	3.5	3.5	−1.4

Abbreviations: ETDRS, Early Treatment of Diabetic Retinopathy Study; VEGF, vascular endothelial growth factor.

and 2.9 in years 3 through 5. VA outcomes in eyes that maintained follow-up over 5 years showed worsening of vision in all treatment groups, with a loss of 1.4 letters in treated eyes and a loss of 3.1 letters in untreated eyes. Treated eyes managed with anti-VEGF monotherapy had the least loss in VA (0.6 letters) over 5 years (Table 2).

Conclusions

This study sought to identify shifting patterns of DME treatment among US retina specialists. We found that over 5 years, there was a clear trend toward greater use of intravitreal anti-VEGF monotherapy, less laser monotherapy, and fewer untreated eyes. These real-world outcomes were derived from an established database of aggregated, longitudinal EMRs that represent a geographically and demographically diverse group of patients examined by US retina specialists.

A year-to-year comparison of 2015 and 2020 showed a rise in the use of anti-VEGF monotherapy (43.5% vs 61.8%; $P <$ .001). At the same time, there was a decrease in the use of focal laser therapy, whether as monotherapy (9.7% vs 3.0%; $P <$ .001) or in combination as follows: anti-VEGF + laser, 9.7% vs 3.5% ($P <$ .001) and anti-VEGF + steroid + laser, 0.8% vs 0.1% ($P <$ .001).

There was an increase in aflibercept use from 2015 to 2020 (38.0% of total anti-VEGF use to 45.0%), which could have been influenced by results from Protocol T, whose 1-year results published in 2015 showed better outcomes with aflibercept in patients with worse initial vision.[11] Laser monotherapy use decreased from 2015 to 2020 (9.7% vs 3.0%), and only 5.4% of eyes followed over 5 years were treated with laser monotherapy. VA gains in treated eyes remained stable at 1 year in 2015 and 2020 (3.6 letters vs 3.5 letters).

There are limitations to this study that are intrinsic to a retrospective database analysis. Specifically, the International Classification of Diseases lacks specific coding to distinguish between clinically significant or center-involving diabetic edema. There are also no imaging data in the database that can be used to verify and quantify the severity of DME. Although our analysis attempted to identify newly diagnosed DME without a history of prior treatment, a previous diagnosis and/or treatment at another practice or distant treatment before data collection cannot be excluded. Furthermore, we did not specifically analyze switches in agents in the anti-VEGF monotherapy group and did not record whether combination therapy was simultaneous or sequential. Finally, vision data were based on VA measurements collected in routine clinical practice and not on best-corrected VA, as obtained in clinical trials, and should be interpreted with appropriate caution.

Although our study suggests that there was cumulative vision loss for patients with 5 years of follow-up between 2015 and 2020, it is important to consider the limitations of assessing real-world retrospective data in this database, which can be controlled for in randomized clinical trials. As seen in other real-world studies, these limitations include periodic loss to follow-up and cataract formation from intravitreal and periocular steroids.[15–18] There may also be a component of selection bias because patients being managed for 5 years and patients on combination therapy could have a more severe degree of retinopathy that was not controlled for. Nonetheless, our study highlights the importance of recognizing that differences exist between functional outcomes in clinical trials vs real-world conditions.

In conclusion, this study shows an evolution in DME treatment patterns among US retina specialists. The practice patterns align with conclusions from major randomized DME clinical trials. We hope to use these data to empower ophthalmic platforms to better understand current and future treatment patterns for DME.

Ethical Approval

This project was considered exempt from institutional review board review because the research involved the collection of existing de-identified data.

Statement of Informed Consent

Informed consent was not required for this study.

Declaration of Conflicting Interests

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