Thieme

Diabetic Macular Oedema – Patient Characteristics and the Reality of Treatment in a German University Hospital

Das diabetische Makulaödem – Patientenkollektiv und Behandlungsrealität in einem deutschen Universitätsklinikum

Authors
Anna Mareike Eder, Walter Sekundo, Volker Besgen, Stephan Schulze

Affiliation
Klinik für Augenheilkunde, Universitätsklinikum Gießen und Marburg – Standort Marburg, Deutschland

Keywords
pharmacology, retina, diabetic macular oedema, IVOM therapy

Schlüsselwörter
Retina, diabetisches Makulaödem, IVOMs, Pharmakologie

received	17.5.2024
accepted	16.9.2024
published online	18.11.2024

Bibliography
Klin Monatsbl Augenheilkd 2025; 242: 22–29
DOI 10.1055/a-2419-1794
ISSN 0023-2165

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Anna Mareike Eder
Klinik für Augenheilkunde, Universitätsklinikum Gießen und Marburg – Standort Marburg
Baldingerstraße, 35033 Marburg, Deutschland
Phone: + 49 (0) 16 01 84 17 84
annamareike.eder@gmx.de

ABSTRACT

Background Diabetic macular oedema (DME) is associated with significant loss of visual acuity. Intravitreal VEGF inhibitor injection is the gold standard in treating this disease; second-line treatment consists of intravitreal steroid injections. This treatment has already undergone extensive investigation in large randomised controlled trials. The aim of this study is to evaluate patient population and treatment options in a real-world setting.

Material and Methods A retrospective analysis was conducted on data from 176 eyes in 114 patients diagnosed with diabetic macular oedema who had received at least one intravitreal injection during 2018 at Marburg University Hospital Department of Ophthalmology. The analysis examined demographic characteristics, prior treatment, and treatments performed as well as visual acuity and central retinal thickness development during therapy. Multiple linear regression analyses were used to investigate the influence of different variables on changes in dependent variables in visual acuity (logMAR), changes in retinal thickness (µm), and number of injections, while also taking interactions between the independent variables themselves into account.

Results Patients were on average 64.45 ± 13.79 years old and predominantly male (61.93%). Most (71.59%) had already been treated for DME. Baseline visual acuity averaged 0.42 logMAR ± 0.34; baseline central retinal thickness averaged 369.1 µm ± 118.81. A total of 688 intravitreal injections were administered at 3.91 ± 2.22 per eye during the study period. Visual acuity improved by 0.04 logMAR ± 0.18 on average; eyes with poorer baseline visual acuity showed a greater increase in visual acuity. CRT values decreased by 44.54 µm ± 133.95 on average. Eyes with higher baseline values showed greater reduction. Using regression analysis, this is the first study to demonstrate that eyes may continue to require additional injections after prior treatment.

Conclusion This study demonstrated the reality of treatment for patients with diabetic macular oedema at a German university clinic as accurately as possible. We were able to demonstrate the differences from RCTs and the characteristics of the patient cohort.

ZUSAMMENFASSUNG

Hintergrund Das diabetische Makulaödem (DMÖ) ist mit einem relevanten Visusverlust assoziiert. Den aktuellen Goldstandard zur Behandlung dieser Erkrankung stellen intravitreale Injektionen mit einem VEGF-Inhibitor dar, die Zweitlinientherapie eine Behandlung mit intravitrealen Steroiden. Diese Therapie wurde in großen randomisierten Studien bereits umfangreich untersucht. In dieser Arbeit sollen die Patientinnen und Patienten sowie die Therapiemöglichkeiten in einem Real-World-Setting evaluiert werden.

Material und Methoden Es wurden Daten von 176 Augen von 114 Patienten der Augenklinik des Universitätsklinikums Marburg, die im Jahr 2018 mindestens eine intravitreale Injek-

tion bei der Diagnose DMÖ erhalten haben, retrospektiv ausgewertet. Untersucht wurden dabei demografische Charakteristika, Vorbehandlung, durchgeführte Therapien sowie die Entwicklung des Visus und die der zentralen Netzhautdicke. Mithilfe multipler linearer Regressionsanalysen wurde der Einfluss der verschiedenen Variablen auf die abhängigen Variablen Visusänderung (logMAR), Netzhautdickenänderung (µm) sowie Injektionsanzahl untersucht. Dabei wurden ebenso die Einflüsse der Variablen untereinander berücksichtigt.

Ergebnisse Patienten waren durchschnittlich 64,45 ± 13,79 Jahre alt und überwiegend männlich (61,93 %). Mit 71,59 % war ein Großteil bereits bez. des DMÖs vorbehandelt. Der Ausgangsvisus lag bei durchschnittlich 0,42 logMAR ± 0,34, der Ausgangswert der zentralen Netzhautdicke bei 369,1 µm ± 118,81. Im beobachteten Zeitraum wurden insgesamt 688 intravitreale Injektionen verabreicht, pro Auge durchschnittlich 3,91 ± 2,22. Es zeigte sich eine durchschnittliche Visusverbesserung um 0,04 logMAR ± 0,18, wobei Augen mit einem schlechteren Ausgangsvisus eine stärkere Visuszunahme verzeichneten. Bezüglich des CRT-Wertes kam es zu einer durchschnittlichen Reduktion um 44,54 µm ± 133,95. Augen mit einem höheren Ausgangswert zeigten eine stärkere Reduktion. In den Regressionsanalysen konnte außerdem erstmalig gezeigt werden, dass bereits vorbehandelte Augen weiterhin vermehrt Injektionen benötigen könnten.

Fazit In dieser Arbeit konnte die Behandlungsrealität des DMÖs in einem deutschen Universitätsklinikum detailliert dargestellt werden. Es konnte aufgezeigt werden, welche Unterschiede zu RCTs existieren und was das Patientenkollektiv charakterisiert.

Introduction

Diabetic retinopathy (DR) is one of the leading causes of blindness amongst working-age adults across the world [1], whereby diabetic macular oedema (DME) is the main cause of visual loss in DR [2]. DME involves increased blood sugar levels leading to changes in retinal small blood vessels; this may lead to increased vascular permeability compromising the blood-retinal barrier, causing extracellular fluid and proteins to leak into the macula, potentially leading to macular swelling [3, 4]. This process involves vascular endothelial growth factors (VEGFs), cytokines, and inflammatory reactions [5, 6].

Diabetes prevalence is expected to increase across the world [7]. The prevalence of DME is also expected to increase, emphasising the importance of adequate ophthalmological treatment for this disease.

Various studies have shown VEGF to play a major pathophysiological role in increasing vascular permeability in retinal vessels. This may lead to the DME development. VEGF concentrations in diabetic eyes correlate significantly with oedema severity [5, 6, 8–10]. These observations have made a substantial contribution to the increasing importance of intravitreal VEGF inhibitors in DME treatment. The substances used in the clinical setting at the time of the study were ranibizumab (Lucentis, Novartis, Basel, Switzerland), aflibercept (Eylea, Bayer, Leverkusen, Germany) and bevacizumab (Avastin, Roche, Basel, Switzerland) [11]. Intravitreal steroids are administered as second-line treatment in the form of a long-term injectable remaining in the bulbus [12]. The substances used are dexamethasone (Ozurdex, Abbvie, Ludwigshafen, Germany) and fluocinolone acetonide (Iluvien, Alimera Sciences Europe Limited, Dublin, Ireland). Triamcinolone may also be administered as an off-label medication [12–15].

Numerous large randomised controlled trials (RCTs) have already studied the effectiveness of intravitreal operative medication or IVOM therapy. Most patients show significant improvement in visual acuity and a significant decrease in central retinal thickness (CRT) [16–20]. In addition, the superiority of IVOM therapy using VEGF inhibitors in DME treatment has been demonstrated compared to focal laser therapy alone [16–18].

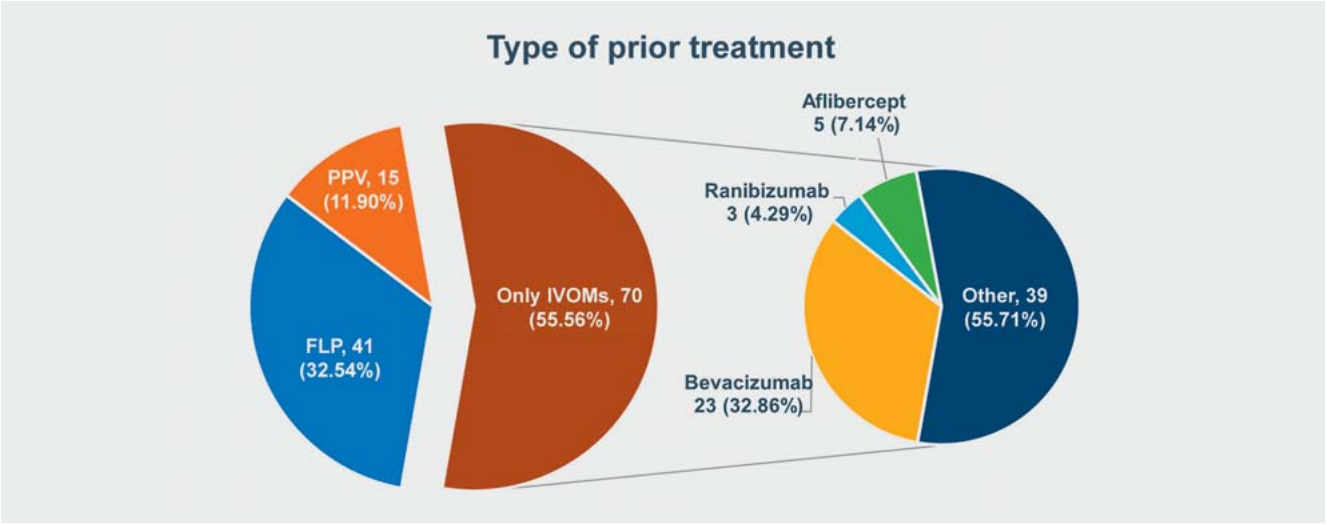
However, these RCTs can only be applied to an everyday clinical setting to a limited extent for a variety of reasons. One of these reasons lies in the patient cohorts in the RCTs: Many of these RCTs on DME treatment include very tight exclusion criteria such as pre-existing conditions, HbA1c values, and baseline visual acuity values. Applying the results from these RCTs to an everyday clinical setting is therefore problematic, as these usually involve physicians treating a far more heterogeneous patient cohort [12, 16–21].

Real-world studies (RWSs) on DME treatment have also shown significant improvements in visual acuity using intravitreal VEGF inhibitors. However, these changes are less pronounced than those found in RCTs. Real-world settings have also shown lower injection numbers compared to RCTs [22–25].

This demonstrates that results from IVOM therapy in patients with DME in everyday clinical practice differ from those in approval studies. One explanation could be the more heterogeneous patient pool, such as patients with previous ocular diseases, poorly controlled diabetes, or more diverse visual acuity values. In addition, the lower number of injections indicates looser compliance with treatment plans.

However, these RWSs also only reflect clinical reality to a limited extent. Some of these studies also imposed strict inclusion criteria. For example, two only included patients without prior DME treatment [26, 27] and two excluded patients who had previously been administered VEGF inhibitors [23, 28]. This does not match the reality of everyday clinical settings with many patients treated after several prior DME treatments. Additionally, none of the above RWS covered all three VEGF inhibitors to treat DME, instead limiting treatment to one or two of the three substances used in a clinical setting at the time [22–25]. RWSs treating DME with dexamethasone implants paint the same picture [13, 29].

To our knowledge, there is a lack of generalisable data realistically reflecting clinical practice in DME treatment, so this study retrospectively analysed patients with DME requiring treatment within one calendar year at a university hospital. The aim was to reflect the reality of this patient cohort and the clinical treatment administered to these patients at a university hospital as authentically as possible.



▶ **Fig. 1** Types of prior treatment in all previously treated eyes (n = 126). The circle on the right shows the exact medications received by eyes given IVOM therapy only. Diagrammbeschriftung [diagram label]: Type of prior treatment, absolute number (percentage).

Methods

We performed a retrospective analysis on 176 eyes in 114 patients having undergone at least one IVOM therapy after being diagnosed with diabetic macular oedema at Marburg University Hospital in 2018. Eyes with improvement or deterioration in visual acuity due to eye surgery performed independently of DME as well as eyes that suffered vitreous haemorrhage during the study period were excluded from the analysis. There were no specific inclusion or exclusion criteria beyond that.

We collected patient data for statistical analysis comprising gender (female/male), age (years), current HbA1c value (%), prior treatment (none, intravitreal injections, laser, pars plana vitrectomy), intravitreal injections performed during the study period with date and preparation, and any focal laser treatments and operations performed. We also recorded respective visual acuity (logMAR) and CRT values (µm) before and after treatment. Analysis on time intervals between two VEGF inhibitor injections only included eyes that had solely been administered VEGF inhibitor injections.

The eyes were classified into two groups before beginning injections – those with good baseline visual acuity and those with poor baseline visual acuity – to aid statistical analysis between these two groups. The median baseline visual acuity value amongst the eyes evaluated was used for reference to ensure that the two groups were as close to equal in size as possible. This median value was calculated at 0.3 logMAR. Eyes were grouped in the same way for baseline CRT values. The median value was also used as a guide for CRT values and was calculated at 333 µm. The Mann-Whitney U-test in the absence of a normal distribution and independent samples was performed to calculate significance in the group comparison; we used SPSS for the purpose. The Kruskal-Wallis test was performed for comparing several groups.

We investigated the influence of the different variables on visual acuity change (logMAR), retinal thickness change (µm), and number of injections as dependent variables using multiple linear regression analysis. This also took mutual influences of variables on each other into account.

Results

A total of 176 eyes in 114 patients were included in the study. Of the 114 patients, 71 were male (109 eyes; 61.93 %) and 43 were female (67 eyes; 38.07 %). The average age of the patients in this study was 64.45 ± 13.79 years (24–86, median: 67).

HbA1c values were taken for 87 patients (134 eyes; 76.14 %); average value was 7.2 % ± 1.13 (5.5–11.3, median: 7).

Mean baseline visual acuity was 0.44 logMAR ± 0.36, (− 0.08–1.54, median: 0.4).

The mean CRT value was 362.42 µm ± 116.75, (125–790, median: 331).

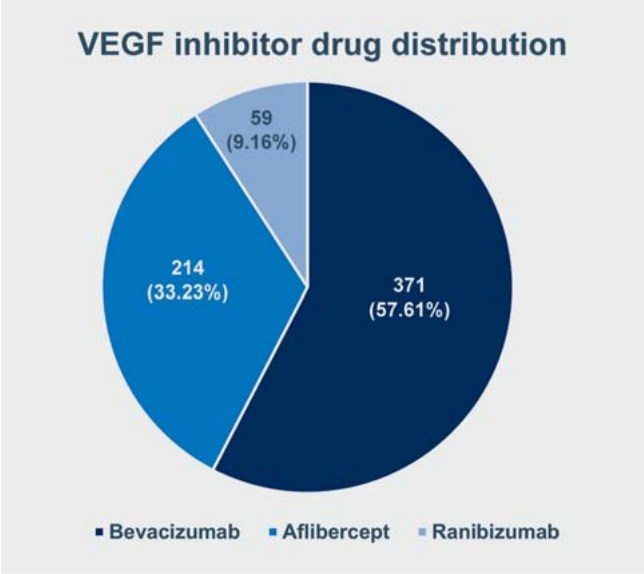
Of the 176 eyes included in the analysis, 126 (71.59 %) had previously been treated for diabetic macular oedema. However, 50 eyes (28.41 %) had not been treated before (▶ **Fig. 1**).

Treatment during the study period

In total, 688 injections were administered during the study period analysed. VEGF inhibitors were administered in 644 cases, steroid injections in 44 (▶ **Fig. 2**). An average of 3.91 ± 2.22 (1–12, median: 3) injections were administered per eye (▶ **Fig. 3**). An average of 36.19 ± 20.73 days (21–203, median: 28) lay between the first and second VEGF inhibitor injections. This was the shortest average interval between two injections at 67.19 ± 40.75 days (28–211, median: 56; ▶ **Fig. 4**).

Outcome

Average visual acuity was 0.42 logMAR ± 0.34 on the first visit (baseline) and 0.38 logMAR ± 0.31 on the last (n = 147) (endpoint). The median was 0.3 in each case. Therefore, average visual acuity improved by 0.04 logMAR ± 0.18.



▶ **Fig. 2** Drug distribution in VEGF inhibitor injections administered (n = 644). Diagrammbeschriftung [diagram label]: Absolute numbers (percentage).

Eyes with poorer baseline visual acuity (> 0.3 logMAR, n = 71) showed greater improvement in visual acuity than eyes with better baseline visual acuity (≤ 0.3 logMAR, n = 75). The former improved by 0.1 logMAR ± 0.22 on average, whereas the latter deteriorated by 0.01 logMAR ± 0.1 on average (▶ **Fig. 5**).

This difference was statistically significant ($p < 0.001$). The medication used did not result in any significant difference in visual acuity development ($p = 0.428$).

The mean baseline CRT value was 369.1 µm ± 118.81 (n = 142). The mean endpoint CRT value was 324.56 µm ± 105.41. Therefore, the result was a reduction of 44.54 µm ± 133.95. Eyes with higher baseline CRT values at the start of treatment (≥ 333 µm, n = 71) showed greater improvement over time at an average reduction of 98.31 µm ± 143.91 compared to eyes with lower baseline values (< 333 µm, n = 71). Eyes with lower baseline values even showed an average increase of 9.24 µm ± 96.92 (▶ **Fig. 6**).

The difference here between the two groups was statistically significant ($p < 0.001$). The medication used did not result in any significant difference in central retinal thickness development ($p = 0.208$).

Regression

Our regression analysis results showed baseline CRT value to have a significant influence on CRT value development over time ($p = 0.001$). Correlation was negative as described above with higher initial CRT values resulting in greater reductions over time. The variables for prior treatment with IVOM therapy compared to no prior treatment ($p = 0.006$), baseline CRT value ($p = 0.001$), and baseline visual acuity value ($p = 0.007$) also showed significant influence on the number of injections as the dependent variable. This model therefore supports the hypothesis that better baseline visual acuity and higher baseline CRT values require a higher number of injections. Prior IVOM therapy was also found to associate with a higher number of injections compared to no prior therapy.

The other variables did not show any statistically significant effect ($p > 0.05$).

Discussion

At a mean age of 64.45 years with 61.93% male patients, the patient cohort in this contribution was demographically similar to those of RWSs and large RCTs [17–20, 30]. Most of the eyes examined (71.59%) had already been treated for DME. Our patient cohort showed average HbA1c values of 7.2% at a minimum of 5.5% and maximum of 11.3%. This indicates slightly better glycaemic control than in other studies [17, 19, 20, 30].

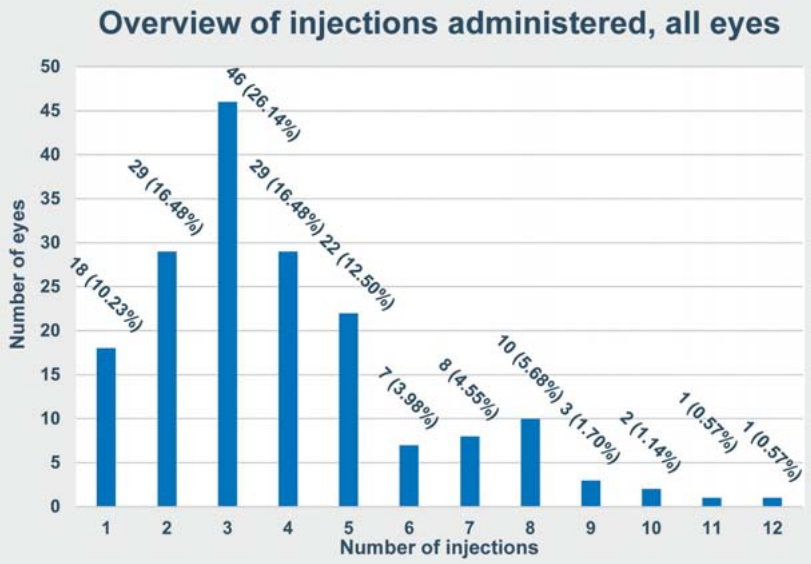
Baseline visual acuity in patients from this study cohort averaged 0.44 logMAR. This corresponds to around sixty-four ETDRS letters, which is better than other RWSs studied [22–24, 27, 28]. Large RCTs reported values between 54.7 and 64.8 letters [17–20.30]. The average value in this contribution was therefore also in the upper range. The mean baseline eye CRT values at 362.42 µm were substantially lower than values from other RWSs [23, 24, 28]. The values in RCTs were also higher (412–540 µm) than in the cohort described here [17–20, 30].

The average number of injections was lower in this study by a wide margin compared to large RCTs if we include only those eyes that had been treated solely using VEGF inhibitors. Here, the numbers of injections ranged between 6.8 and 12.2 in the first year. The most likely explanation for this is that unlike this study, the large RCTs used rigid treatment plans with regular follow-up appointments and a fixed study period [17–20, 30].

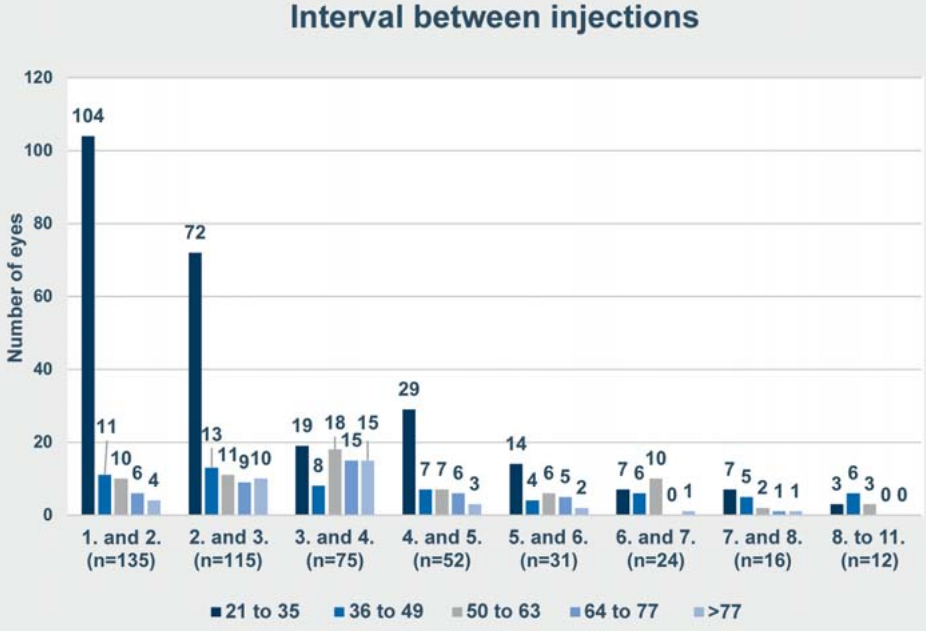
Other RWss showed lower values compared to the RCTs: A large meta-analysis from different RWSs reported an average of 5.3 VEGF inhibitor injections per eye [24]. Stefanickova et al. (2018) documented an average of 4.9 for twelve months excluding any eyes not followed up on for at least twelve months compared to 4.5 including all eyes [23]. The average number of injections applied in this study is rather low [! Unklar, auf welche Studie bezogen evtl “our study” oder “the present contribution], even in comparison to other RWSs. The likeliest explanation for this lies in a difference in approach towards representing the reality of treatment than all other RWSs by focusing mainly on the study period itself rather than on development in individual eyes. Unlike the others, this contribution did not require any minimum observation period for the eyes to be included in the study. Many RWSs only included eyes observed for at least twelve months, often resulting in a greater number of injections [22–24, 27, 28, 30].

Interval between injections

Our results for the interval between two consecutive VEGF inhibitor injections tallies with the data from other RWSs [22, 23, 28]. Average intervals between VEGF inhibitor injections in this contribution had been kept short, especially between the first three injections. Most of the eyes observed were administered subsequent injections within a maximum period of five weeks. However, some of the eyes were not administered subsequent injections until much later.



▶ **Fig. 3** Overview of the number of injections administered for all eyes (n = 176); x-axis: Total number of eye injections over the study period; y-axis: Number of eyes. Balkenbeschriftung [Bar label]: Absolute number of eyes (percentage).



▶ **Fig. 4** Interval between each two injections. Only eyes treated using an VEGF inhibitor were included (n = 135); x-axis: Injections; y-axis: Absolute number of eyes. The subgroups show the interval in days between injections.

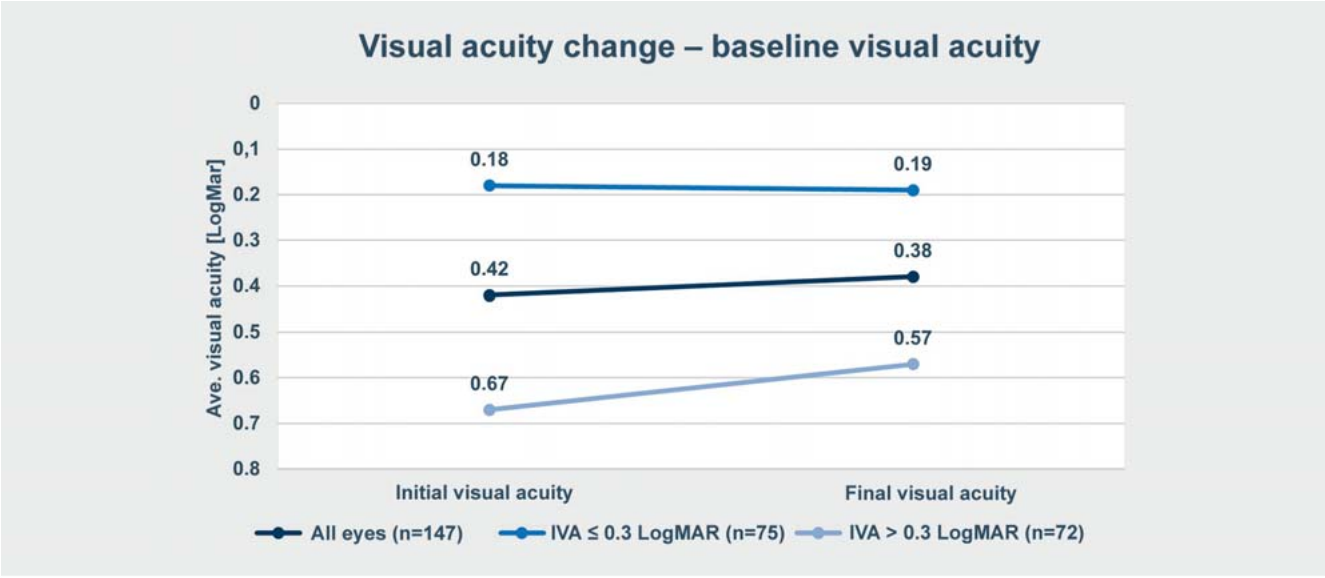
Visual acuity

The average change in visual acuity at an improvement of approximately 2.17 letters observed in this study falls short of results from the RCTs by a wide margin. Average visual acuity improvement ranged between 5.6 and 13.3 letters in these studies [17–20, 30].

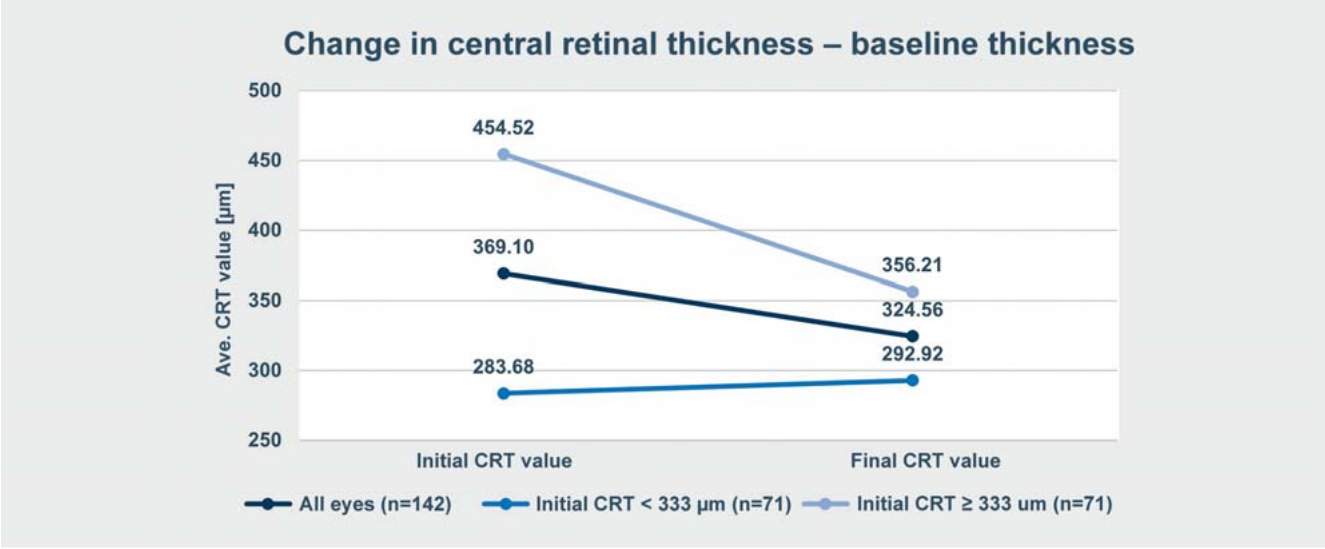
Other RWSs also reported higher overall visual acuity improvement [22–28].

Central retinal thickness

We found an average reduction of 44.54 µm in central retinal thickness development.



▶ **Fig. 5** Change in visual acuity grouped by baseline value. All eyes with a baseline and endpoint visual acuity values available were included (n = 147); x-axis: Time course between baseline and endpoint value; y-axis: Visual acuity. Subgroups: Baseline visual acuity for all eyes, ≤ 0.3 logMAR (better visual acuity) and > 0.3 logMAR (poorer visual acuity). Lower logMAR values indicate better visual acuity; the y-axis is inverted.



▶ **Fig. 6** Average change in central retinal thickness (CRT) grouped by baseline thickness. Eyes with baseline and endpoint CRT values were analysed (n = 142); x-axis: Time course between baseline and endpoint CRT value; y-axis: Mean CRT value. Subgroups: Baseline CRT value.

This value is also substantially lower than those of other studies. RCTs showed reductions between 102 and 169 µm after one year [17, 18, 20, 30]. Other RWSs also showed better results [23, 24].

Interpreting the Results

Compared to other studies, the results of the present contribution differ in both visual acuity and central retinal thickness development. There are several possible reasons for this. On the one hand, other studies imposed substantially tighter inclusion and exclusion criteria [17, 19, 20, 27, 30].

The limited observation period affecting some cases in this contribution could be another reason. Many studies followed up on their patients for at least six to twelve months [17–20, 22–24, 27, 28, 30]. We omitted this condition in our study as our primary goal was to provide as realistic a picture as possible of average DME patients and the treatment received rather than evaluating the effectiveness of a particular treatment. This involved including eyes after far shorter follow-up times in our anal-

ysis. These patients therefore also underwent shorter treatment times and received lower injection numbers. This could be expected to yield less meaningful results.

Even so, it should be borne in mind that the aim of this contribution was to present as realistic a picture as possible of DME patients and treatment in an everyday clinical setting. Viewed alongside other RWSs, these results could help brief patients with realistic expectations on expected outcomes, thus potentially promoting compliance during therapy.

Results from regression calculations

Regression analysis showed a statistically significant negative correlation between baseline CRT values in the study period and the difference in CRT values at the end of treatment.

Parameters with a significant influence on the number of injections were baseline visual acuity value, baseline CRT value, and prior IVOM therapy compared to no prior therapy.

Other studies did not find any association between baseline visual acuity and number of injections [22, 27]. Higher baseline CRT values also showed a positive association with the number of injections administered in this study. However, this was a weak association. To our knowledge, this contribution is the first study to establish an association between higher number of injections and prior treatment with intravitreal injections compared to no prior treatment. Eyes that had already been administered intravitreal injections for DME in the past therefore required additional injections during the course of treatment. Further studies would be necessary to explore how this affects visual acuity and central retinal thickness development. However, it supports the assumption that the DME requires long-term therapy. Corresponding patient briefings to this effect could encourage compliance.

Study Evaluation

This study is subject to limitations. The heterogeneity in our study cohort hindered any clear explanation as to whether the change in visual acuity was due to increased DME activity or another eye disease. Further studies of this kind would be needed for larger data sources. The retrospective nature of the analysis also includes limiting factors.

Even so, this contribution still provided a detailed picture of actual treatment reality for DME patients in the outpatient clinic of a university hospital. To the best of our knowledge, this is the first work to be performed in this way. The few inclusion and exclusion criteria gave rise to an especially faithful representation of everyday clinical practice in Germany.

DME prevalence is high in our society and is expected to continue to rise in the future, so continuous ophthalmic care optimisation and cooperation between physicians and patients would be an important objective. Achieving this would involve collecting data reflecting all patients rather than a highly selective cohort. We have achieved this in this contribution.

Further RWSs could be performed that represent actual conditions and DME patients as this study did without excluding a large proportion of eyes due to previous diseases, previous treatments, and so on. This would allow broad and realistic data collection on DME treatment in everyday clinical settings towards improving patient treatment. This would also enable further investigation on which expectations on visual acuity development are realistic in DME treatment in everyday clinical settings and which factors influence this for physicians to be able to relay these expectations to patients, at best towards maximising patient compliance.

CONCLUSION

Already known:

- IVOM therapy comprising VEGF inhibitors and steroids may improve visual acuity and central retinal thickness in eyes with diabetic macular oedema.
- No clear superiority of any individual drug has yet been clearly demonstrated.

New:

- Actual patient populations in a German university hospital are far more complex than those covered in RCTs. This has an impact on outcome expectations.
- Eyes previously administered intravitreal injections for DME required additional injections during treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Yau JW, Rogers SL, Kawasaki R et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012; 35: 556–564. DOI: 10.2337/dc11-1909

[2] Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984; 91: 1–9

[3] Cohen SR, Gardner TW. Diabetic Retinopathy and Diabetic Macular Edema. Dev Ophthalmol 2016; 55: 137–146. DOI: 10.1159/000438970

[4] Grehn F. Augenheilkunde. 32. Aufl. Heidelberg: Springer; 2019

[5] Nentwich MM, Ulbig MW. Diabetic retinopathy – ocular complications of diabetes mellitus. World J Diabetes 2015; 6: 489–499. DOI: 10.4239/wjd.v6.i3.489

[6] Shaya FT, Aljawadi M. Diabetic retinopathy. Clin Ophthalmol 2007; 1: 259–265

[7] Wild S, Roglic G, Green A et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047–1053. DOI: 10.2337/diacare.27.5.1047

[8] Bandello F, Cicinelli MV, Parodi MB. Anti-VEGF Molecules for the Management of Diabetic Macular Edema. Curr Pharm Des 2015; 21: 4731–4737. DOI: 10.2174/1381612821666150909095756

[9] Boyer DS, Hopkins JJ, Sorof J et al. Anti-vascular endothelial growth factor therapy for diabetic macular edema. Ther Adv Endocrinol Metab 2013; 4: 151–169. DOI: 10.1177/2042018813512360

[10] Fogli S, Mogavero S, Egan CG et al. Pathophysiology and pharmacological targets of VEGF in diabetic macular edema. Pharmacol Res 2016; 103: 149–157. DOI: 10.1016/j.phrs.2015.11.003

[11] Schmidt-Erfurth U, Garcia-Arumi J, Bandello F et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017; 237: 185–222. DOI: 10.1159/000458539

[12] Boyer DS, Yoon YH, Belfort R jr. et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014; 121: 1904–1914. DOI: 10.1016/j.ophtha.2014.04.024

[13] Bucolo C, Gozzo L, Longo L et al. Long-term efficacy and safety profile of multiple injections of intravitreal dexamethasone implant to manage diabetic macular edema: A systematic review of real-world studies. J Pharmacol Sci 2018; 138: 219–232. DOI: 10.1016/j.jphs.2018.11.001

[14] European Medicines Agency (EMA). Ozurdex: EPAR – Product Information (20.07.2022). Im Internet (Stand: 28.09.2023): https://www.ema.europa.eu/en/documents/product-information/ozurdex-epar-product-information_en.pdf

[15] Schmidt-Erfurth U, Garcia-Arumi J, Bandello F et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica 2017; 237: 185–222. DOI: 10.1159/000458539

[16] Brown DM, Schmidt-Erfurth U, Do DV et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology 2015; 122: 2044–2052. DOI: 10.1016/j.ophtha.2015.06.017

[17] Michaelides M, Kaines A, Hamilton RD et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. Ophthalmology 2010; 117: 1078–1086.e2. DOI: 10.1016/j.ophtha.2010.03.045

[18] Mitchell P, Bandello F, Schmidt-Erfurth U et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011; 118: 615–625. DOI: 10.1016/j.ophtha.2011.01.031

[19] Nguyen QD, Brown DM, Marcus DM et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012; 119: 789–801. DOI: 10.1016/j.ophtha.2011.12.039

[20] Wells JA, Glassman AR, Ayala AR et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology 2016; 123: 1351–1359. DOI: 10.1016/j.ophtha.2016.02.022

[21] Campochiaro PA, Brown DM, Pearson A et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology 2012; 119: 2125–2132. DOI: 10.1016/j.ophtha.2012.04.030

[22] Ziemssen F, Wachtlin J, Kuehlewein L et al. Intravitreal Ranibizumab Therapy for Diabetic Macular Edema in Routine Practice: Two-Year Real-Life Data from a Non-interventional, Multicenter Study in Germany. Diabetes Ther 2018; 9: 2271–2289. DOI: 10.1007/s13300-018-0513-2

[23] Stefanickova J, Cunha-Vaz J, Ulbig M et al. A noninterventional study to monitor patients with diabetic macular oedema starting treatment with ranibizumab (POLARIS). Acta Ophthalmol 2018; 96: e942–e949. DOI: 10.1111/aos.13771

[24] Mehta H, Nguyen V, Barthelmes D et al. Outcomes of Over 40,000 Eyes Treated for Diabetic Macula Edema in Routine Clinical Practice: A Systematic Review and Meta-analysis. Adv Ther 2022; 39: 5376–5390. DOI: 10.1007/s12325-022-02326-8

[25] Best AL, Fajnkuchen F, Nghiem-Buffet S et al. Treatment Efficacy and Compliance in Patients with Diabetic Macular Edema Treated with Ranibizumab in a Real-Life Setting. J Ophthalmol 2018; 2018: 4610129. DOI: 10.1155/2018/4610129

[26] Campos Polo R, Rubio Sanchez C, Garcia Guisado DM et al. Aflibercept for clinically significant diabetic macular edema: 12-month results in daily clinical practice. Clin Ophthalmol 2018; 12: 99–104. DOI: 10.2147/OPTH.S154421

[27] Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. Br J Ophthalmol 2021; 105: 216–221. DOI: 10.1136/bjophthalmol-2020-315933

[28] Blinder KJ, Dugel PU, Chen S et al. Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). Clin Ophthalmol 2017; 11: 393–401. DOI: 10.2147/OPTH.S128509

[29] Chhablani J, Bansal P, Veritti D et al. Dexamethasone implant in diabetic macular edema in real-life situations. Eye (Lond) 2016; 30: 426–430. DOI: 10.1038/eye.2015.246

[30] Korobelnik JF, Do DV, Schmidt-Erfurth U et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014; 121: 2247–2254. DOI: 10.1016/j.ophtha.2014.05.006