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Pigment Epithelial Detachment Followed by Retinal Cystoid Degeneration Leads to Vision Loss in Treatment of Neovascular Age-Related Macular Degeneration

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Purpose: Intravitreal antiangiogenic therapy is the major therapeutic breakthrough in neovascular age-related macular degeneration (AMD). Optical coherence tomography (OCT) is the leading diagnostic tool, but solid criteria for optimal therapeutic outcomes are lacking. A comprehensive analysis of structure/function correlations using Food and Drug Administration- and European Medicines Agency–approved substances and fixed and flexible regimens was performed.

Design: Post hoc analysis of a prospective, randomized multicenter clinical trial including 189 study sites.

Participants: A total of 1240 patients with active neovascular AMD.

Methods: Participants received intravitreal ranibizumab or aflibercept. A fixed regimen was used for 48 weeks followed by a flexible regimen until week 96. At monthly intervals, best-corrected visual acuity (BCVA) was measured and retinal morphology was assessed by standardized OCT, including intraretinal cysts (IRCs), subretinal fluid (SRF), and pigment epithelial detachment (PED), presenting with a width $\geq$400 μm or a height of $\geq$200 μm. Results were correlated for each regimen, feature, and time.

Main Outcome Measures: The BCVA outcomes in relation to retinal pathomorphology based on non-inferiority for all treatment arms.

Results: In neovascular AMD, only IRC at baseline and persistent through week 12 had a negative impact on BCVA. With therapeutic intervention, exudative features such as IRC and SRF resolved rapidly in 74% of eyes, whereas PED responded only slowly with 38%. Independent of the type of regimen, fixed or flexible, retinal morphology correlated tightly with visual function. Intraretinal cysts consistently showed the lowest BCVA gains with either regimen or substance. With the switch from a fixed to a flexible pro re nata (PRN) regimen, progressive visual loss occurred exclusively in the group with primary PED presenting as the hallmark of neovascular activity and was induced by secondary formation of IRC in the neurosensory retina.

Conclusions: The efficacy of antiangiogenic therapy in neovascular AMD is strongly determined by morphologic features. The subretinal pigment epithelium lesion underlying PED appears to be the primary indicator for progressive disease activity, whereas secondary cystoid degeneration is the most relevant imaging marker for visual function. Clinically, PED emerged as trigger for consecutive vision loss in PRN treatment. *Ophthalmology 2015;122:822-832 © 2015 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) has become a major medical and socioeconomic challenge throughout the world. It is the leading cause of legal blindness affecting 10% to 13% of adults aged >65 years in North America and other genetically similar populations, such as those in Europe and Australia and recently Asia.[1,2] Its incidence is expected to at least double by 2020 on the basis of worldwide increased life expectancy alone.[3] With the substantial increase in other known risk factors such as smoking and obesity, the AMD incidence is set to increase exponentially.[4,5] The Global Burden of Disease Study 2010 announced that vision loss accounted for 21.1 million years lived with disability. The study also recorded a steep increase of 158.9% in vision-related years lived with disability due to AMD alone between 1990 and 2010.[6] Disability due to AMD has a profound effect on quality of life, with an impact similar to AIDS, chronic renal failure, and stroke representing an immense and growing burden of disease for individuals and societies.[7]

However, medical research is an impressive example of a game-changer among widespread disorders. The management of neovascular AMD has recently been revolutionized by the identification of its pathophysiologic mechanisms, particularly the role of vascular endothelial growth factor

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(VEGF).[8,9] In AMD, overexpression and binding of VEGF-A to its receptors on endothelial cells lead to increased vascular permeability and fluid leakage into the neurosensory retina, and support progressive proliferation of neovascular nets resulting in invasive subretinal growth. Inhibition of VEGF-A can efficiently block the pathologic process and restore morphology and function of the retina.[10] Ranibizumab, an affinity-enhanced, humanized anti-VEGF-A antibody fragment, provided pioneering proof-of-principle of the clinical efficacy of anti-VEGF therapy in neovascular AMD in landmark trials.[11,12] Since the approval of ranibizumab in 2006, characteristics of the burden of AMD disease have changed completely.[13] Intraocular pharmacotherapy has significantly reduced the prevalence of legal blindness and visual impairment due to AMD.[14]

The potential benefit of antiangiogenic therapy has since been confirmed in many communities, but with results uniformly below clinical trial.[15] The management of AMD faces a huge dilemma, because only intensive monthly re-treatment regimens offer optimal outcomes and flexible strategies are associated with inferior results.[16–18] Moreover, strict monthly monitoring is recommended for pro re nata (PRN) strategies, although consistent morphologic features have not been identified to guide treatment.[19] Simultaneously, costs of approved drugs are exploding, making ocular anti-VEGF intervention one of the highest financial drains in medicine consecutively affecting overall budgets, with too many interventions, patients, and visits.[20–22] The burden of disease has turned into a burden of care in an area of abundant prevalence in a growing portion of the global population.

Currently, 2 anti-VEGF substances are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA): the antibody ranibizumab and aflibercept, a soluble decoy receptor, binding with high-affinity to all VEGF-A and VEGF-B isoforms, as well as to placental growth factor.[10,23,24] Recently, aflibercept and ranibizumab were both successfully used in the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) studies providing proof of clinical noninferiority of either substance in the largest therapeutic AMD trial ever performed.[23,24] Moreover, the VIEW trial includes not only both approved substances but also both major regimens, a fixed and a flexible as-needed schedule: A total of 2457 patients with neovascular AMD received a fixed re-treatment every month/every other month regimen for 48 weeks, followed by a flexible OCT-guided PRN regimen during weeks 52 to 96. A standardized monthly monitoring schedule was used to measure visual function and to identify structural changes using optical coherence tomography (OCT).[25] The large size and comprehensive design of the trial offer a unique opportunity to evaluate the effects and mechanisms of antiangiogenic therapy using the currently EMA- and FDA-approved anti-VEGF substances with respect to the EU (flexible) and US (fixed) label-based regimens and to finally identify solid imaging markers relevant for therapeutic outcomes in clinical practice. Analysis and correlation of functional and morphologic changes were performed by an independent OCT-reading center with the aim of identifying clinically and prognostically relevant factors that provide solid guidance for an efficient, practical, and affordable management of neovascular AMD in the near future and establish OCT in routine procedures and budgets in a global setting.

Methods

The VIEW2 study was a randomized, double-masked, active-controlled, multicenter, 96-week phase 3 trial monitoring efficacy and safety of intravitreal aflibercept and ranibizumab in patients with neovascular AMD. Its full protocol and main outcomes have been published.[23] The ethics committee at the Medical University of Vienna and each institutional review board or ethics committee at the international study sites approved the study protocols. The trial was registered with ClinicalTrials.gov (identifier no NCT00637377), and all patients signed a written consent form before initiation of the study-specific procedures. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria have been described.[23] In brief, patients aged 50 years or older with untreated, active, subfoveal choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to neovascular AMD were eligible for enrollment, if CNV covered at least 50% of total lesion size and best-corrected visual acuity (BCVA) was between 25 and 73 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. All lesion types in the concomitant age group and with the concomitant visual acuity levels were included, offering a representative population in AMD disease from 4 continents.

Treatment Regimens

Patients were randomized to receive 0.5 mg intravitreal ranibizumab or 0.5 mg/2 mg intravitreal aflibercept every 4 or 8 weeks after 3 initial monthly injections. During the follow-up period from weeks 52 to 96, patients received a flexible PRN regimen with monthly evaluations for interim injections based on prespecified re-treatment criteria. These were new or persistent fluid on OCT, an increase in central retinal thickness (CRT) of 100 μm or more, loss of 5 ETDRS letters or more in conjunction with recurrent fluid on OCT, new-onset classic neovascularization, new or persistent leakage on fluorescein angiography, new macular hemorrhage, or a time lapse of 12 weeks since the previous injection. Dosages and intervals were all found to be clinically equivalent and statistically noninferior for all groups.[23,24]

Functional and Morphologic Parameters

Patients were examined every 4 weeks through 96 weeks. Each visit included a detailed BCVA assessment by masked, certified vision examiners using ETDRS-like charts and anterior/posterior segment examination. Stratus OCT (Carl Zeiss Meditec, Dublin, CA) scans were acquired monthly by masked, certified operators using the fast macular thickness map (FMTM) scan mode for quantitative measures of CRT and the 6-mm cross-hair scan mode for qualitative assessment of retinal morphology. The FMTM protocol acquired six 6-mm radial lines consisting of 128 A-scans per line, whereas the cross-hair protocol acquired two 6-mm lines (0° and 90°) with a resolution of 512 A-scans per line.

The Vienna Reading Center, an independent digital reading center, evaluated OCT images to provide a uniform, standardized assessment of defined retinal morphology for each visit of all

patients. Validated computer-assisted grading software was used. This software imports OCT raw scan data and allows the reader to grade multiple variables in the FMTM- and 6-mm cross-hair scans following a defined algorithm. All OCT images underwent a standardized, comprehensive grading for relevant disease-specific morphologic criteria in a validated, cross-reading center-consistent fashion.[26] The 6-mm cross-hair scan was used for morphologic analysis. Most important, independently of the protocol-based procedures, predefined ancillary parameters were introduced reflecting distinct changes at each of the 3 (sub-)retinal compartments: presence or absence of intraretinal cysts (IRCs), subretinal fluid (SRF), and pigment epithelial detachment (PED) involving the center point. Intraretinal cysts were defined as round, minimally reflective spaces within the neurosensory retina. Subretinal fluid was identified as a nonreflective space between the posterior boundary of the neurosensory retina and the retinal pigment epithelium (RPE)/choriocapillaris signal. Pigment epithelial detachment was defined as a focal elevation of the reflective RPE band over an optically clear or moderately reflective space with a minimum width of 400 μm at the base or a minimum height of 200 μm from the surface of the RPE band to the surface of the choriocapillaris.

Multiple levels of quality-control programs were performed to maintain intergrader reproducibility. The readers were trained according to the Vienna Reading Center protocol, and certification was awarded on successful completion of all requirements. Difficulties in grading were handled through regular supervision sessions with the grading leader in which selected images were discussed with the group's input. In addition, we selected a random sample of 10% of scans for quality control with subsequent independent review by the supervisor.

Statistical Analysis

The original main outcomes of the VIEW trial (noninferiority of aflibercept to ranibizumab) has been published.[23] Noninferiority of the treatment arms allowed pooling of all participants into a single population and enabled integrated analysis of morphologic subgroups in the current study. Only the VIEW2 population was used because monthly OCT examinations were not mandated per protocol in VIEW1. This was an exploratory study of a comprehensive clinical trial database. Thus, no formal hypotheses were formulated and no sample size calculations were performed.

Categoric variables are described as numbers with percentage (N, %). Continuous variables are summarized with their mean, standard deviation, median, minimum, and maximum. Differences between categoric variables were tested using the Cochran–Mantel–Haenszel test, and for continuous variables the Wilcoxon rank-sum test was used.

Predictive models were constructed to predict visual acuity at baseline, change from baseline to week 12/week 52 (fixed regimen), and change from week 52 to week 96 (flexible regimen). These outcomes were predicted using a mixed linear model, with OCT parameters at baseline, week 12, week 52, or during year 1 or the PRN phase, and baseline BCVA, wherever appropriate, as fixed effects or independent (predictive) variables. To stratify the analyses for the 4 different treatment regimens, and thus to ensure that the observed effects of the fixed effects were consistent throughout the whole study population, the assigned treatment arm was entered as a random variable. On the basis of the primary noninferiority of all substances and the (bi-) monthly administration, statistical power could be increased by pooling the datasets within each regimen.[23,24] All analyses were performed using SAS version 8.2 (SAS Inc, Cary NC).

Results

Morphologic Features at Baseline and Correlation with Visual Function

Of the 1240 patients included, 1202 were available for intention-to-treat analysis.[23] Baseline analysis of morphologic features found that 64.4% of eyes had IRCs, 80.1% of eyes had PED, and 84.1% of eyes had SRF (Fig 1). Intraretinal cyst was the only morphologic feature that correlated statistically significantly with baseline BCVA, that is, in untreated disease (Table 1). Baseline vision was reduced by a mean of -5.98 ± 0.85 letters ($P < 0.0001$) with the presentation of IRC, reflecting a pronounced alteration in neurosensory function. When IRCs were still present 3 months after the treatment started, there was an additional correlation amounting to a further reduction in BCVA by -3.92 ± 1.04 letters ($P = 0.002$). Subretinal fluid at 12 weeks was associated with less reduction in initial mean BCVA.

Therapeutic Effects during the Loading Interval: Morphology, Function, and Predictive Value

The morphologic response was apparent rapidly, with substantial recovery seen in all 3 compartments after the first 3 injections (Fig 2). However, although baseline IRC and SRF, secondary exudative features, resolved in 74% of eyes after the first 3 doses, PED did so in only 38% of eyes. After month 3, all anatomic changes reached a plateau phase with residual IRC and SRF seen at rates half of that of PED throughout both the fixed and the flexible PRN regimens. At month 3, BCVA improved overall by a mean of $+10.37\pm0.8$ letters, but baseline neurosensory IRC and subretinal PED were associated with a negative impact on BCVA with a loss of 1.97 ($P = 0.0017$) and 2.27 ($P = 0.015$) letters, respectively (Table 2). Baseline BCVA per se and in combination with the presence of IRC also had a significant effect on the functional benefit seen after the first 3 monthly doses, with less improvement at higher BCVA levels.

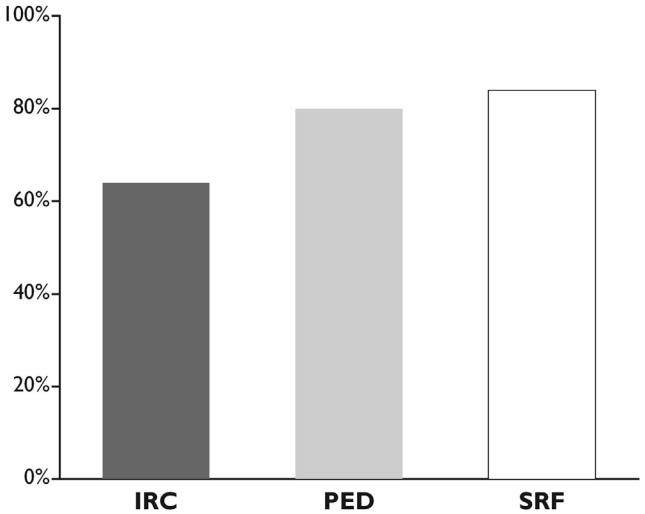

Figure 1. Baseline disposition of morphologic variables. Intraretinal cysts (IRC) represent intraretinal fluid, pigment epithelial detachment (PED) reflects any elevation of the retinal pigment epithelium (RPE) of at least 400 μm in width or 200 μm in height, and subretinal fluid (SRF) refers to pooling of clear SRF.

Table 1. Multivariate Model: Impact of Morphologic Features on Baseline Best-Corrected Visual Acuity

Morphologic Parameter	BCVA Estimate ± SE (Letters)	*P* Value
Intercept	56.10±0.84	<0.0001
Cysts at baseline	−5.98±0.85	<0.0001
Cysts at week 12	−3.92±1.04	0.0002
SRF at week 12	+4.05±0.97	<0.0001

BCVA = best-corrected visual acuity; SE = standard error; SRF = subretinal fluid.
Initial and persistent cysts have an additive negative effect on retinal function in untreated neovascular age-related macular degeneration. Intercept refers to the mean BCVA condition without morphologic alteration.

Resolution and Recurrence of Intraretinal Cysts during and after Loading Phase

Of 412 patients without IRC at baseline, only 171 (41.5%) were found to have IRC at any point during the first year (Fig 3A). Baseline IRC that had resolved by 3 months rarely recurred during the 1-year follow-up of continuous treatment (Fig 3B). Approximately 50% of such patients exhibited no further findings of IRC, and 80% of eyes had IRC observed less than 3 times. These cysts resolving during the loading interval, the phase of active resolution, were referred to as "exudative" cysts as distinct from cysts that persisted >3 months, which were considered degenerative cysts. Patients with persistent IRC seen consecutively at week 12 had a higher recurrence rate with half of the patients showing 5 or more recurrences indicating progressive disease activity despite continuous treatment (Fig 3C).

Impact of Retinal Morphology on Best-Corrected Visual Acuity under a Fixed Regimen

The BCVA values at every time point correlated with baseline retinal morphology. When the individual morphologic subgroups were stratified according to the prognostically relevant features, such as presence or absence of IRC, SRF, or PED, patients with IRC had the lowest BCVA values. In contrast, patients with SRF only, and no IRC or PED, had the best BCVA values (Fig 4A). Of note, this correlation between structure and function was entirely independent of the therapeutic regimen and continued throughout the entire follow-up period even when the fixed regimen was changed to a PRN strategy. Within the IRC group, persistent degenerative cysts at 3 months were associated with an even lower visual function (Fig 4B).

Prognostic Features for Long-Term Best-Corrected Visual Acuity Outcome under a Fixed Regimen

With a fixed therapeutic regimen over 48 weeks, the presence of IRC (−3.85±0.84, $P < 0.0001$) and PED (−2.12±0.97, $P = 0.028$) at baseline was predictive of a negative outcome (Table 3). Again, the initial BCVA value alone ($P < 0.0001$) or combined with IRC ($P = 0.003$) had a robust influence on visual outcome. Visual gains were generally higher with lower baseline BCVA and lower with better initial BCVA. Most important, the influence of BCVA was strongly dependent on the underlying morphologic features and was again worse with IRC. At lower baseline BCVA values, the common condition in patients with AMD, final BCVA outcomes differed greatly between the morphologic groups, whereas at higher initial BCVA values retinal morphology was less important (Fig 5).

Morphology and Function under a Flexible Pro Re Nata Regimen

The tight association between morphologic alteration and retinal function persisted between weeks 52 and 96 under a flexible regimen (Fig 4A). As seen previously with a fixed schedule, neurosensory IRC, particularly together with PED, had a negative impact on BCVA outcomes. Accordingly, persistent cysts were consistently associated with poor visual acuity levels (Fig 4B) independently of a fixed or a flexible type of regimen. However, with regard to changes in BCVA, distinct features became evident at the time of switching from a continuous to a discontinuous regimen. Although other morphologic groups remained functionally stable, eyes with PED, especially those without previous cysts, showed a progressive decline in visual function (Fig 6A). Sensitivity analysis showed that the occurrence of IRC associated with BVCA loss was distinctly restricted to the time of switching to a PRN regimen at week 52 and beyond. Further analysis of this group revealed that the

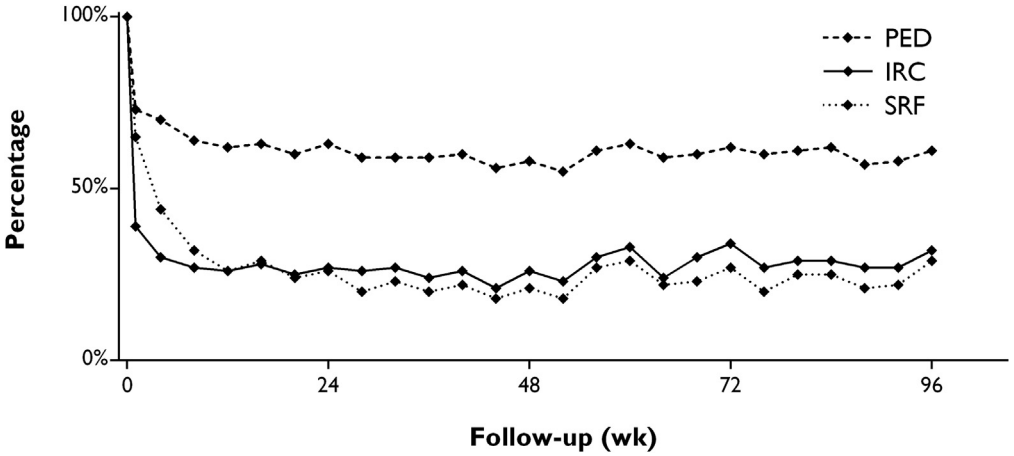

Figure 2. Morphologic response of individual compartments to treatment initiation and maintenance. At month 3, intraretinal fluid and subretinal fluid (SRF) have resolved substantially, whereas the majority of pigment epithelial detachments (PED) are resistant to anti-vascular endothelial growth factor therapy. Beyond this loading interval, the mean frequency of fluid pooling remains unchanged. IRC = intraretinal cyst.

Table 2. Multivariate Model: Predictive Factors for Best-Corrected Visual Acuity Change from Baseline to Week 12

Morphologic Parameter	BCVA Estimate ± SE (Letters)	*P* Value
Intercept	10.37±0.81	0.0010
Cysts at baseline	−1.97±0.62	0.0017
PED at baseline	−2.27±0.72	0.0015
BCVA at baseline (letters, centered on 52)	−0.20±0.04	<0.0001
Interaction between cysts at baseline and BCVA at baseline (letters, centered on 52)	+0.13±0.04	0.0028

BCVA = best-corrected visual acuity; PED = pigment epithelial detachment; SE = standard error.
Baseline IRCs and PEDs were associated with a negative impact on BCVA and the baseline level of BCVA.

progressive decline in BCVA during flexible therapy was driven by the patients with primary PED who developed secondary IRC when switching to PRN (Fig 6B). This BCVA decline was statistically significant from weeks 52 to 96.

Role of Pigment Epithelial Detachment and Cysts during Long-Term Follow-up

Monitoring the change in PED occurrence over time indicated that, although the incidence of PED had declined during continuous therapy, the switch to a discontinuous regimen led to a reactivation in PED, that is, the subretinal lesion. Simultaneously, there was a close correlation between the BCVA change and the frequency of cyst occurrence in those eyes with PED (Table 4). This coincidence implies that PED recurrence was the primary event of neovascular reactivation, but that secondary neurosensory cystic degeneration is the morphologic manifestation of functional loss. This is supported by the finding that eyes with PED lesions and a low frequency of cyst occurrence improved more under both regimens, whereas those in which cyst formation increased showed significantly more visual loss from −1.1 to −4.4 letters between weeks 52 and 96. The corresponding scatter plot highlights the linear correspondence between cyst frequency and BCVA change (Fig 7). The functional benefit declined with an increasing frequency of cysts formation.

Discussion

The management of AMD is a brilliant example for the vital role of imaging markers in a disease that has a global dimension, a growing prevalence, and a lifelong need for therapeutic control, as is true for many medical conditions in the developed world. In the absence of solid imaging markers, the transfer of clinical study success into clinical routine will fail,[15] outcomes on a large scale will be disappointing, and excessive resources will be spent inefficiently. Moreover, despite large scientific studies, misconceptions about therapeutic mechanisms and prognostic factors may be protracted further and prevent the introduction of efficient management guidelines and the development of superior therapeutic strategies.

In the current study, the role of retinal morphology in antiangiogenic therapy of neovascular AMD was for the first time analyzed systematically in a large multiethnic population for an extensive follow-up period. Patients were treated intravitreally with the 2 available FDA- and EMA-approved substances: ranibizumab and aflibercept. On the basis of proven noninferiority of the compounds and the (bi-) monthly regimens, the statistical power for morphologic subgroup analysis could be substantially enhanced to reliably identify prognostic signals.[23,24] The 2 approved therapeutic strategies according to the EU and US label, that is, a fixed monthly and a flexible PRN regimen, were evaluated. Strict monthly functional and morphologic monitoring procedures were applied whereby visual acuity was measured by certified examiners and prespecified morphologic features in OCT were identified by an independent reading center.

First, a strong association among distinct morphologic features, visual outcome, and prognosis was revealed, when functional and structural results were correlated. At all time points, IRCs had a negative impact on visual function. Whenever cysts occurred, at baseline or during therapy, visual acuity was significantly compromised. This phenomenon was independent of whether the therapeutic regimen was continuous or discontinuous and was even

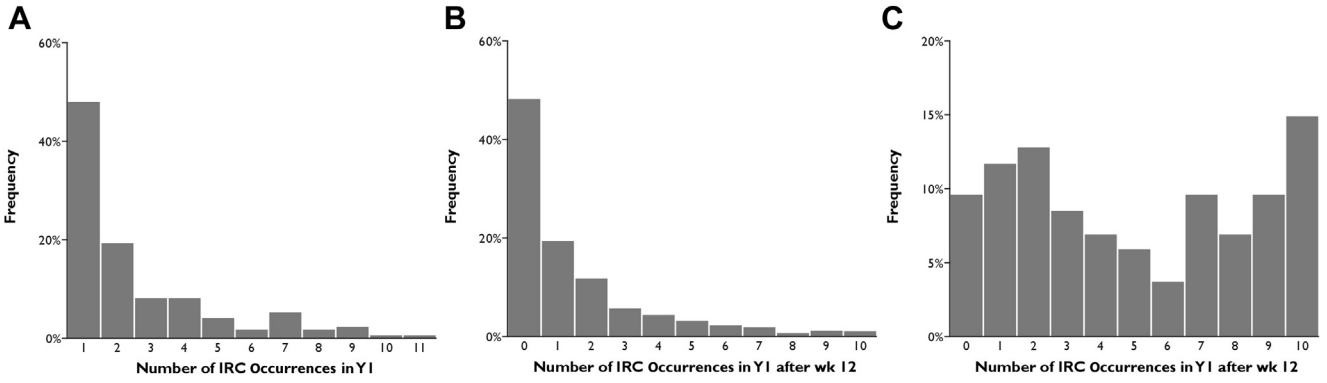

Figure 3. Recurrence of intraretinal cysts (IRCs) during maintenance treatment by response at week 12. **A,** Occurrence of IRC in patients without IRC at baseline, with <50% of patients developing cysts at any time during year 1. **B,** Baseline IRC that had resolved by 3 months rarely recurred during the 1-year follow-up of continuous treatment. **C,** Patients with IRC seen at baseline and consecutively at week 12 had a higher recurrence rate, with half of the patients showing ≥5 recurrences. Y1 = year 1.

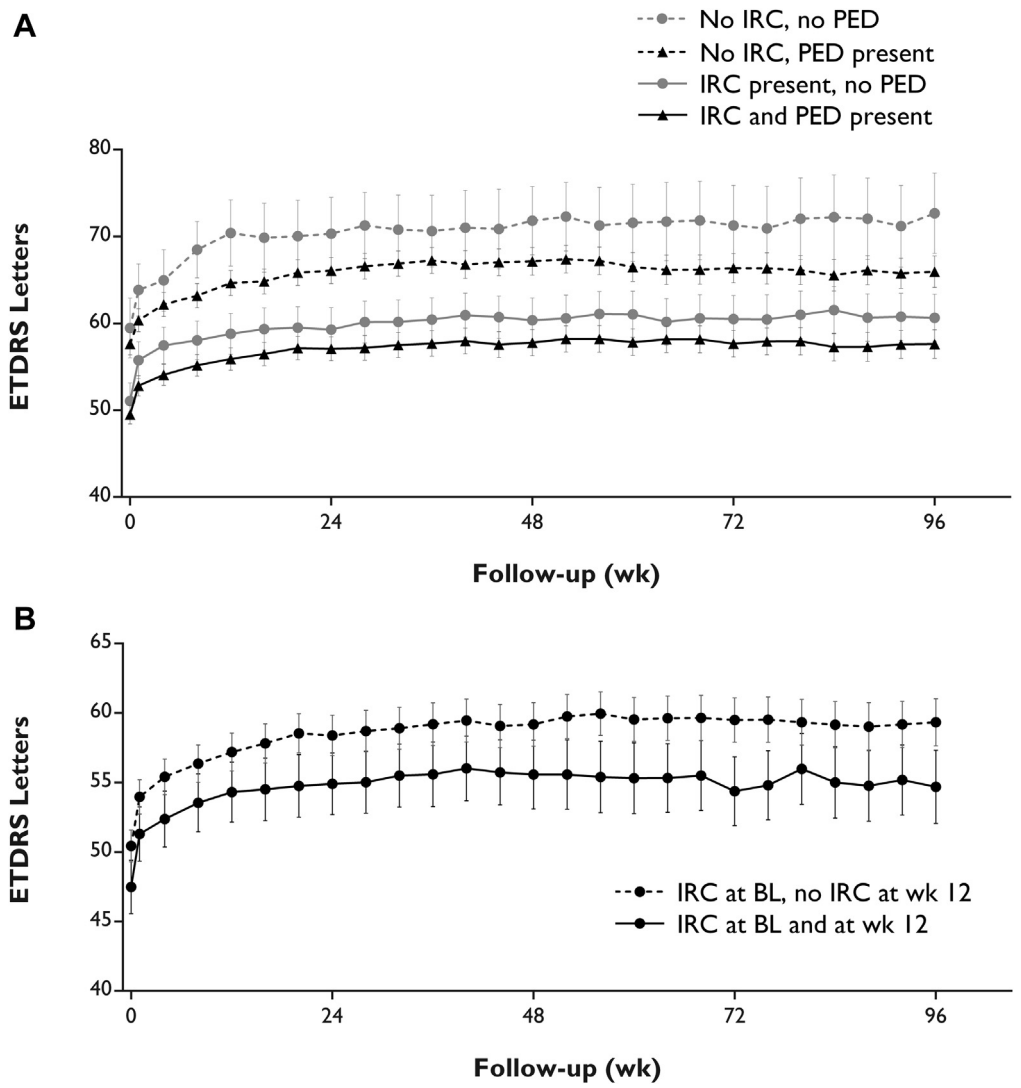

Figure 4. A, Impact of retinal morphology on best-corrected visual acuity (BCVA) levels at baseline and during follow-up. Intraretinal cysts were consistently associated with the lowest BCVA values, whereas subretinal fluid (SRF) only and no intraretinal cyst (IRC) or = pigment epithelial detachment (PED) demonstrated the best BCVA values. This correlation was independent of the type of regimen (fixed/flexible). **B,** Comparison of BCVA outcomes between treatment-responsive and unresponsive cysts. Persistent cysts were associated with lower BCVA values compared with cysts resolving during the loading phase and were therefore referred to as "degenerative" cysts. ETDRS = Early Treatment Diabetic Retinopathy Study.

Table 3. Multivariate Model: Predictive Factors for Best-Corrected Visual Acuity during a Fixed Treatment Regimen

Morphologic Parameter	BCVA Estimate ± SE (Letters)	*P* Value
Intercept	65.54±1.07	<0.0001
Cysts at baseline	−3.85±0.84	<0.0001
PED at baseline	−2.12±0.97	0.0284
BCVA at baseline (letters, centered on 52)	+0.65±0.05	<0.0001
Interaction between cysts at baseline and BCVA at baseline (letters, centered on 52)	+0.22±0.06	0.0003

BCVA = best-corrected visual acuity; PED = pigment epithelial detachment; SE = standard error.
Initial presence of IRCs and PED and a higher baseline BCVA levels were associated with a negative prognosis.

more pronounced in the low vision range typically seen in patients with AMD. Degenerative cysts, which persisted throughout the initial loading phase, at the level of the neurosensory retina showed the worst prognosis in terms of visual outcomes. The frequency of the occurrence of cysts finally determined the visual outcome.

Second, unstable visual function was maintained during PRN therapy despite a flexible reduction in re-treatment frequency, with the exception of eyes with a primary subretinal pathology. Pigment epithelial detachment recurred and progressed under a discontinuous PRN regimen. An elevation of the RPE layer is directly associated with the activity of the neovascular component originating from the underlying choriocapillary bed; thus, PED is the direct hallmark of neovascular disease. Sub-RPE lesion activation precedes the consecutive IRC formation that is associated

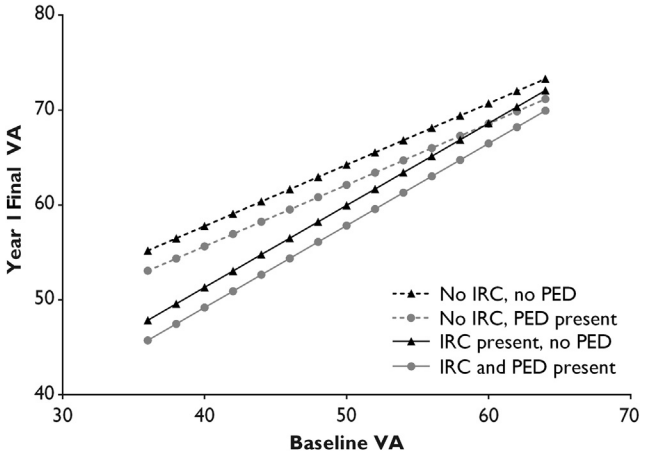

Figure 5. Correlation of baseline best-corrected visual acuity (BCVA), baseline morphology, and BCVA outcomes. The impact of individual morphologic features on visual function increased significantly with lower BCVA levels. IRC = intraretinal cyst; PED = pigment epithelial detachment; VA = visual acuity.

with progressive functional loss after the switch from a fixed to a flexible regimen.

These are the most important 2 messages from our study: Our findings identify PED as the most relevant parameter reflecting progressive disease activity and provides the link between the primary lesion activity morphologically (by sub-RPE activity) and the consecutive loss of retinal function (by neurosensory cysts). It also clearly contradicts the current convention that PRN and OCT-guided therapy are generally less effective than the more burdensome and cost-intensive fixed treatment strategy. This dogma of an overall deficiency of the PRN approach has been promoted repeatedly in the literature regarding fixed versus flexible regimens in AMD therapy.[18–20,22] Our analysis proves that this supposed disadvantage was merely the result of gross averaging of outcome data throughout small populations and a lack of identification of valid imaging markers with PED being excluded from the equation.

This study impressively highlights the relevance of defining morphologic features on the basis of solid imaging for evaluating treatment strategies, making prognostic

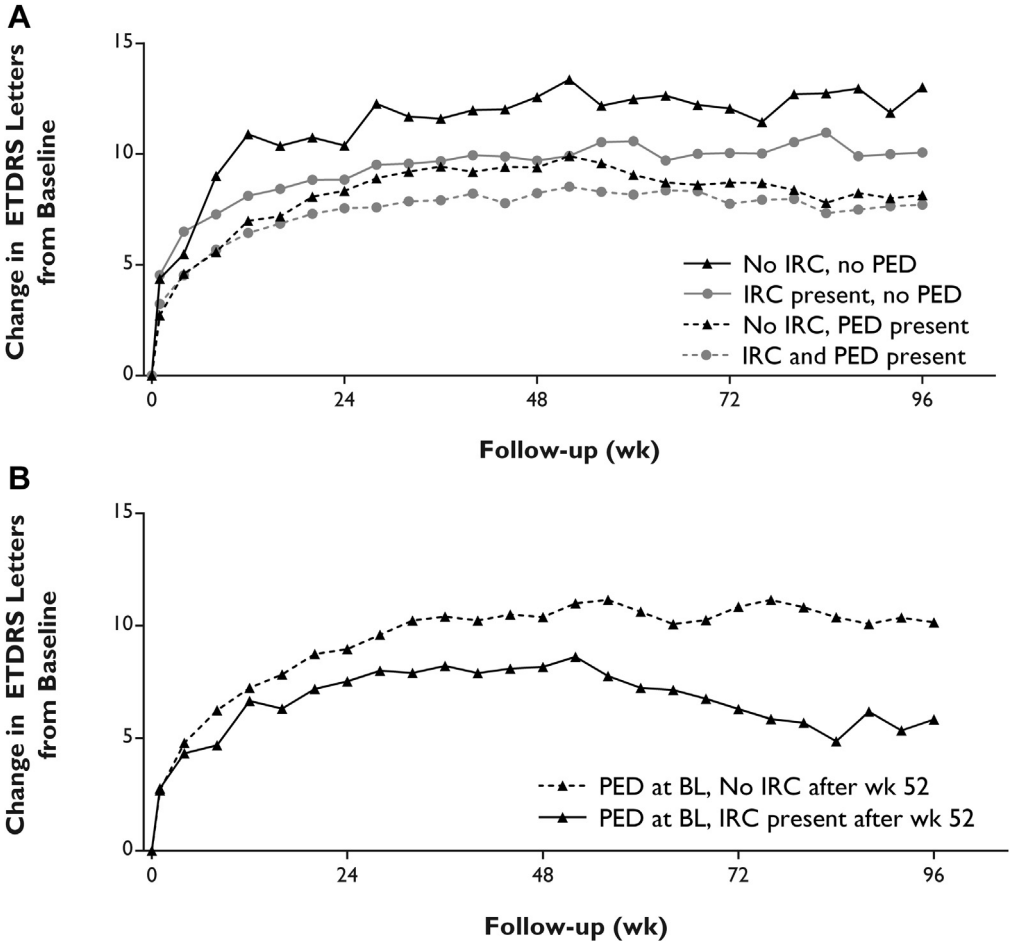

Figure 6. A, Change in best-corrected visual acuity (BCVA) by baseline morphologic status. With the switch from a fixed to a flexible regimen at week 48, eyes with pigment epithelial detachment (PED) and PED/intraretinal cyst (IRC) progressively lost visual function. **B,** Change in BCVA in patients with PED at baseline by IRC status. Patients with PED at baseline secondarily developed IRC during discontinuous pro re nata (PRN) treatment, which is associated with progressive BCVA loss. BL = baseline; ETDRS = Early Treatment Diabetic Retinopathy Study.

Table 4. Correlation between Best-Corrected Visual Acuity Change and Frequency of Cyst Occurrence after the Switch to Discontinuous Treatment in Patients with Pigment Epithelial Detachment at Baseline

No. of Cyst Occurrences in Year 2	No. of Patients	BCVA at Baseline	BCVA Week 52	BCVA Week 96	BCVA Change Baseline to Week 52	BCVA Change Week 52 to Week 96	Mean No. of Cyst Occurrences in Year 2
None	182	58.7	69.6	68.5	10.9	−1.1	0.0
1–2	85	55.0	65.5	61.7	10.5	−3.8	1.4
3–4	31	57.7	67.3	64.8	9.6	−2.5	3.3
5+	27	58.2	58.7	54.3	0.7	−4.4	7.6

BCVA = best-corrected visual acuity.
With increasing cyst formation, BCVA loss is more pronounced.

decisions, and planning socioeconomic investments in a large entity such as AMD. The potential benefit of any medical treatment largely depends on the efficiency of early disease diagnosis and adequate monitoring. Optical coherence tomography is unprecedented in providing in vivo high-resolution visualization of retinal and RPE pathology.[27,28] Therefore, recent multicenter trials investigating anti-VEGF therapy in neovascular AMD have included OCT imaging in their protocols. In 2007, Prospective OCT Imaging of Patients with Neovascular AMD Treated with intraocular Ranibizumab (PrONTO) study the pilot OCT study, suggested that CRT should guide re-treatment decisions.[29] The quantitative criterion of CRT was used for analysis in all subsequent clinical trials.[16,17,20,22] However, our group showed that CRT correlates only with BCVA at baseline and that there is no association between retinal function and thickness beyond 3 months.[25] Visual acuity has consistently and regularly been found to decrease during CRT-guided therapy, and real-world PRN treatment is publicly considered as inferior to monthly re-treatment.[15,20,22]

Evidence that qualitative criteria such as fluid in the 3 different compartments (intraretinal, subretinal, and sub-RPE) offer a more reliable correlation with visual function is just being discovered.[25,30] In the recent Comparison of AMD Treatment Trials (CATT) "any fluid" seen on OCT triggered re-treatment with a "no tolerance" protocol; nevertheless, the PRN regimen showed a morphologic and functional deficit.[20] In VIEW, the indication for re-treatment was diffusely referred to as "new or recurrent fluid on OCT" without focus on the type and location of fluid. Of note, PED as a harbor of exudative and neovascular activity has so far not been named as a relevant imaging marker for recurrence. In the current analysis, PED activation emerges as the primary underlying trigger for loss of vision in a PRN regimen, with a significant loss in this subgroup versus the nonsignificant 1- to 2-letter loss noted by averaging through the entire population.

On initiation of treatment in VIEW, the antipermeability effect of antiangiogenic therapy was rapid and substantial, but there were large differences between the morphologic groups. Although IRC and SRF resolved in 70% to 80% of eyes, PED resolved in less than half of all affected eyes. Most interesting, and in contrast to the current literature, even with continuous interventions, visual outcomes strongly correlated with morphologic features. Although eyes with only SRF showed excellent BCVA values and improvements, eyes with cysts with or without PED started and continued with lower BCVA throughout continuous and discontinuous therapy. So far, better functional results generally have been expected for all patients with strict monthly re-treatment, but the VIEW analysis shows an

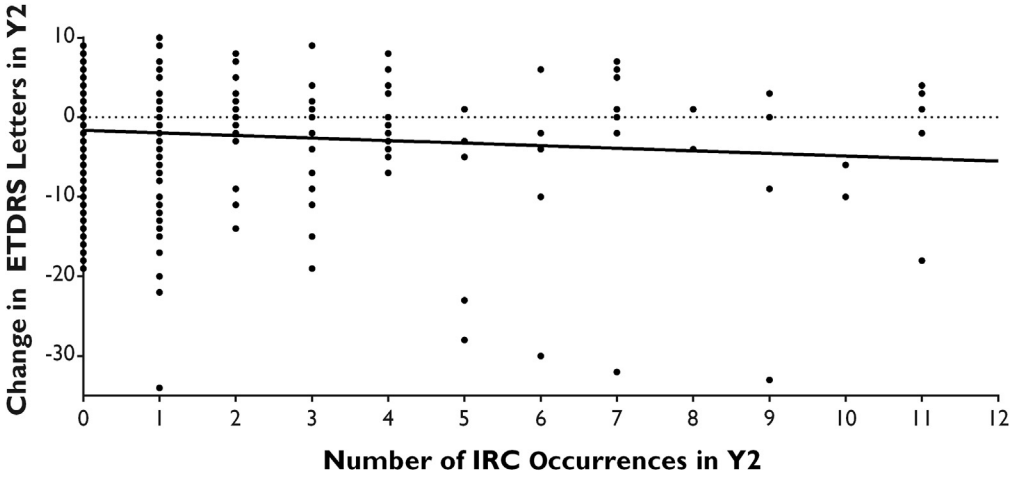

Figure 7. Impact of intraretinal cyst (IRC) recurrence on final best-corrected visual acuity (BCVA) outcomes. Vision loss correlates with the frequency of cyst occurrence. ETDRS = Early Treatment Diabetic Retinopathy Study; Y2 = year 2.

overwhelming effect of distinct morphologic features on VA outcomes even during most intensive VEGF inhibition. Thus, distinct anatomic findings are of substantial value for prognosis in clinical practice and for designing future clinical trials.

The sequential pathway from PED activity to cyst formation to visual loss appears to be characteristic for neovascular AMD. In CNV, disruption of the external limiting membrane photoreceptor complex in the outer retina results in the accumulation of fluid in neurosensory layers.[31] Discontinuities in the inner segment–outer segment (IS-OS) photoreceptor junction are visible using advanced OCT.[32] Loss in visual function has been associated with alterations in the IS-OS line in neovascular AMD.[33] Conventional time-domain OCT is unable to resolve IS-OS features, but the association of outer retinal alteration and IRCs can be examined with advanced spectral-domain OCT and will further elucidate the pathomechanism in AMD disease and therapeutic intervention.

Intraretinal cysts were found to represent a key feature for prognostic evaluation. Subanalysis of transient cysts and persistent cysts revealed that persistent cysts differ from the entire entity because their negative impact on visual function is even stronger. The CATT investigators speculated that non-VEGF–mediated mechanisms, such as apoptosis or necrosis, account for such cystoid spaces.[30] We assume that these persistent cystoid changes are consistent with permanent cystoid degeneration as seen in chronic edema due to long-lasting subretinal exudation.[34] Topographic determination of retinal sensitivity demonstrated profound functional loss of 0 dB at sites with IRCs.[35]

The results of trials published so far suggest that PRN generally results in an outcome pattern with lower overall BCVA.[15,18,20,22] Stratification of PRN results based on retinal morphology in a large population such as in VIEW, however, indicates that the majority of eyes maintain a constant visual benefit. It is the PED group that seems to drive the therapeutic disadvantage of PRN management. This novel observation finally resolves the controversy about prognostic determinants and PRN failure. Neovascular AMD originates from the choroid, penetrates Bruch's membrane, and proliferates in the sub-RPE space or subretinal space. Fibrovascular growth together with vascular leakage produce an elevation of the overlying RPE barrier, which protrudes to a greater or lesser extent depending on lesion activity. In time-domain OCT imaging, the high reflectivity of the RPE band precludes visualization of the PED content. Future technologies such as enhanced depth imaging will allow recognition of the fibrovascular internal structure.[36] Currently, PED is not a recommended parameter for re-treatment protocols in clinical routine or scientific studies, an issue that should be readdressed on the basis of our findings. In VIEW, visual loss progressed with uncontrolled sub-RPE lesion activity in the PRN regimen. Because PED was not considered a relevant re-treatment criterion according to protocol and clinical consensus, adequate timing of reinjections was missed and cystoid retinal degeneration proceeded unabated toward irreversible visual loss.

The biologic impact of anti-VEGF therapy on the primary neovascular component, antiproliferation, and on the secondary exudative component, antipermeability, is a major topic of controversy. The VIEW analysis demonstrates a slow and incomplete resolution of PED in contrast to other morphologic entities despite use of the most effective anti-angiogenic substances and regimen.[37] Although reductions in retinal fluid were impressive, PED volume tended to remain unchanged or to regress only slowly in CATT.[30] Indocyanine green angiography, which visualizes sub-RPE neovascularization, showed no regression in the neovascular lesion area under ranibizumab therapy.[38] Therefore, it has been suggested that antiangiogenic therapy in the eye is not antineovascular, but merely antiexudative with resolution of fluid in and underneath the retina, and persistence of the proliferative lesion. Current clinical management and future therapeutic developments must recognize this deficiency to optimize long-term outcomes.

Study Limitations

A limitation of this study is the use of time-domain OCT only allowing analysis of the 6-mm cross-hair scan mode instead of a large set of tightly spaced raster scans as offered by spectral-domain technology. Nevertheless, solid results were obtained, clearly indicating the path for future analysis. Obviously, novel trial designs are needed to support the assumptions made regarding the functional correlation and prognostic value of the identified parameters, because the VIEW study protocol was not designed to analyze structure/function correlation. It is merely due to the large volume of this unique dataset that such conclusions could be achieved.

Retinal angiomatous proliferation lesions were not excluded by protocol in VIEW or any of the previous studies in neovascular AMD and antiangiogenic therapy. Scott and Bressler[39] identified 10% retinal angiomatous proliferation lesions in the Verteporfin in Photodynamic Therapy trial, but suggested that the response of retinal angiomatous proliferation lesions to CNV treatments may be similar to that of other variants of neovascular AMD. In a recent article by Jung et al,[40] the proportion of retinal angiomatous proliferation lesions in newly diagnosed CNV was as high as 28% to 34%. Retinal angiomatous proliferation lesions may initially present with a combination of PED together with cystic changes in the overlying retina, features consistent with a poor prognosis. However, the focus in our study was on persistent PED, which subsequently presents secondary development of irreversible cystoid retinal degeneration associated with permanent visual loss during a discontinuous therapeutic strategy. Freund et al[31] suggested the use of a hybrid fluorescein angiography/OCT imaging modality to identify the neovascular component underlying sub-RPE lesions. Such a hybrid system will soon be available by the introduction of Doppler OCT enabling identification of vascular and RPE pathologies in a single "multi-modal OCT" approach.[41]

In conclusion, the VIEW data are the largest controlled data pool available in standardized treatment of neovascular AMD. The large population and the fact that all treatment arms in the VIEW2 study, which is the global portion of the study, performed equally allow for the first time to perform solid and statistically relevant subgroup analyses. In

addition, many more predefined parameters were studied than in any previous trial. The finding that the most important factor driving the outcomes is not the type of substance or the type of regimen, but the morphology of the sub-RPE/PED lesion represents a breakthrough. Moreover, OCT as the most relevant diagnostic tool is not even mentioned in the drug labels nor has OCT been recognized by the FDA or EMA as a biomarker tool. In most countries, OCT is currently not even reimbursed. Therefore, extensive analysis highlighting the vital need of OCT for treatment management of the leading ocular disease of current times is essential for the community, for patients around the globe, and for overall healthcare and budget givers.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of AMD Treatment Trials; **CNV** = choroidal neovascularization; **CRT** = central retinal thickness; **EMA** = European Medicines Agency; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FDA** = Food and Drug Administration; **FMTM** = fast macular thickness map; **IRC** = intraretinal cyst; **IS-OS** = inner segment-outer segment; **OCT** = optical coherence tomography; **PED** = pigment epithelial detachment; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **SRF** = subretinal fluid; **VEGF** = vascular endothelial growth factor; **VIEW** = VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD.

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