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Predictors of visual outcomes in patients with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor therapy: *post hoc* analysis of the VIEW studies

Paolo Lanzetta,[1] Alan F. Cruess,[2] Salomon Y. Cohen,[3] Jason S. Slakter,[4] Todd Katz,[5] Olaf Sowade,[6] Oliver Zeitz,[6] Christiane Ahlers[6] and Paul Mitchell[7]

[1]Department of Medicine – Ophthalmology, University of Udine, Udine, Italy
[2]Department of Ophthalmology & Visual Sciences, Dalhousie University, Halifax, Nova Scotia, Canada
[3]Ophthalmological Center for Imaging and Laser, Paris, France
[4]Vitreous Retina Macula Consultants of New York, New York, New York, USA
[5]Bayer US LLC, Whippany, New Jersey, USA
[6]Bayer AG, Berlin, Germany
[7]Department of Ophthalmology, Westmead Institute, University of Sydney, Sydney, New South Wales, Australia

ABSTRACT.

Purpose: **Identify predictors for response to anti-vascular endothelial growth factor (VEGF) therapy in patients with neovascular (wet) age-related macular degeneration (nAMD).**

Methods: **Retrospective, *post hoc* analysis of VIEW 1/2. Patients were randomized 1:1:1:1 to 0.5 mg intravitreal aflibercept (IVT-AFL) injection every 4 weeks (0.5q4); 2 mg IVT-AFL every 4 weeks (2q4); 2 mg IVT-AFL every 8 weeks (2q8) after an initial three injections at weeks 0, 4 and 8 or 0.5 mg intravitreal ranibizumab every 4 weeks (0.5q4).**

Results: **1815 patients [IVT-AFL 2q4 (n = 613); IVT-AFL 2q8 (n = 607); ranibizumab 0.5q4 (n = 595)] were included. Baseline demographics/characteristics were evenly balanced. Younger age (49–69 years), lower visual acuity (VA) [10.0–≤45.0 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] and smaller choroidal neovascularization (CNV) size [0.0–≤3.1 disc areas (DA)] at baseline were associated with the most vision gain (≥15 letters) over 52 weeks (all nominal p < 0.0001).Younger age, higher baseline VA (>64.0–≤83.0 letters) and smaller CNV size were associated with a VA ≥20/40 at week 52. Predominantly classic CNV at baseline (nominal p = 0.0007), older age (≥90 years), lower baseline VA (10.0–≤ 45.0 ETDRS letters) and larger CNV size (>10.1–≤32.6 DA) were all associated with a VA ≤20/200 at week 52 (all nominal p < 0.0001). Along with treatment (nominal p < 0.0001), lower VA (p = 0.0166) and smaller central retinal thickness (both nominal p = 0.0190) were predictors for dry retina development.**

Conclusion: **Younger age, lower VA and smaller CNV size at baseline were all associated with greater vision gains over 52 weeks while younger age, higher VA and smaller CNV size at treatment start were more likely to achieve best-corrected VA 20/40 or better after a year's treatment, suggesting the benefit of early anti-VEGF treatment.**

Key words: aflibercept – anti-vascular endothelial growth factor – neovascular age-related macular degeneration – predictors

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Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss and blindness in industrialized countries (Congdon et al. 2003), with the most severe vision loss occurring in patients with the neovascular ('wet') form (nAMD). Choroidal neovascularization (CNV) and associated retinal oedema are key characteristics of nAMD and targets for treatment.

While treatment options for nAMD can include laser ablation and photodynamic therapy with verteporfin, the current standard of care comprises the use of anti-vascular endothelial growth factor (VEGF) agents, that is, intravitreal aflibercept [IVT-AFL (or VEGF Trap-Eye)], ranibizumab, pegaptanib and bevacizumab. Since their introduction, patients have benefitted from improvements in both functional and anatomical outcomes over several years, while the number of patients diagnosed as legally blind has decreased (Berg et al. 2017; Westborg et al. 2017). However, concerns surrounding potential side-effects of anti-VEGF agents, as well as the burden of monthly visits required for some treatments, have led to efforts to decrease injection and monitoring frequency. Both monthly ranibizumab and bimonthly IVT-AFL are approved for the treatment of nAMD and have been shown to be effective treatment options for patients with this condition (Brown et al. 2006; Rosenfeld et al. 2006; Heier et al. 2012).

Not every patient with nAMD responds well to anti-VEGF therapy and some patients may still lose VA during or after treatment. A number of factors have been shown to play a role in a patient's response to anti-VEGF treatment, including patient age, various lesion characteristics, disease duration, baseline VA and presence of particular genotype risk alleles (Boyer et al. 2007; Ying et al. 2013; Finger et al. 2014; Tsilimbaris et al. 2016).

As different treatment options for nAMD are available, it is of value to patients, physicians and policymakers to determine the likelihood that a patient may respond to a particular drug. The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and VIEW 2) studies were similarly designed, prospective, randomized, double-masked, multicentre, parallel-group, active-controlled phase III trials (Heier et al. 2012) that compared two dosage regimens of IVT-AFL with ranibizumab. At week 52, patients in both the IVT-AFL and ranibizumab treatment groups had similar visual, morphological and safety outcomes (Heier et al. 2012). While these data are invaluable, there remains a need for an increased evidence-based approach regarding predictors of treatment response with anti-VEGF drugs.

The aim of the current analysis was, therefore, to evaluate data from the VIEW studies in order to identify predictive factors of treatment response in patients with nAMD who have been treated with IVT-AFL or ranibizumab.

Patients and Methods

Study design

This was an exploratory, *post hoc* analysis of 1-year data from the VIEW 1 and VIEW 2 studies (Heier et al. 2012). The primary end-point of these studies was the non-inferiority (margin of 10%) of IVT-AFL to ranibizumab in the proportion of patients maintaining vision at week 52 [loss of <15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters]; the VIEW studies have been described in full previously (Heier et al. 2012). Predictors for visual outcomes and retinal dryness are reported here.

Patients

Men and women aged ≥50 years with active, subfoveal or juxtafoveal CNV lesions secondary to AMD were eligible for inclusion in VIEW 1 and 2. Patients with CNV comprising at least 50% of total lesion size, and best-corrected VA (BCVA) between 73 and 25 ETDRS letters (20/40–20/320 Snellen equivalent), were included, while those with prior treatment for neovascular AMD in the study eye were excluded.

Treatment

In VIEW 1 and 2, patients were randomized 1:1:1:1 to 0.5 mg IVT-AFL every 4 weeks (0.5q4); 2 mg IVT-AFL every 4 weeks (2q4); 2 mg IVT-AFL every 8 weeks (2q8) after an initial three injections at weeks 0, 4 and 8; or 0.5 mg intravitreal ranibizumab every 4 weeks (0.5q4). However, as 0.5 mg aflibercept is neither approved nor marketed in any indication, only the IVT-AFL 2q4, IVT-AFL 2q8 and ranibizumab 0.5q4 treatment groups were investigated in this *post hoc* analysis.

Objectives

The objectives of this *post hoc* analysis were to identify predictors for various responses to anti-VEGF therapy at week 52 and to quantify influences from each predictor on the probability of various outcomes of anti-VEGF therapy at week 52.

Response variables

In this exploratory, *post hoc* analysis, we evaluated the following outcome measures: (i) ≥15 ETDRS letter gain; (ii) ≥15 ETDRS letter loss; (iii) any VA loss (≥1 ETDRS letters); (iv) BCVA ≥20/40; (v) BCVA ≤20/200 and (vi) dry retina (i.e. absence of intraretinal and subretinal fluid).

Baseline age (49–69, 70–79, 80–89, ≥ 90 years), CNV size [0.0–≤3.1, >3.1–≤ 6.0, >6.0–≤10.1, >10.1–≤32.6 disc areas (DA)], CNV type (predominantly classic, minimally classic, occult), BCVA (>64.0–≤83.0, >56.0–≤64.0, >45.0–≤56.0, 10.0–≤45.0 ETDRS letters), central retinal thickness (CRT) (103.0–≤245.0, >245.0–≤304.0, >304.0–≤383.0, >383.0–≤868.0 μm), race (white/non-white), sex (female/male), lesion location (subfoveal, extra-juxtafoveal) and treatment group (IVT-AFL 2q4, IVT-AFL 2q8, ranibizumab 0.5q4) were used as explanatory variables in this analysis.

Statistical analysis

Patients included in the full analysis set (FAS) were evaluated. The FAS was defined as all randomized patients who received any study medication and had a baseline and one or more postbaseline BCVA assessment.

Binary (categorical) outcomes measures (≥15 ETDRS letter gain/loss/any VA loss from baseline to week 52, BCVA ≥20/40 or BCVA ≤20/200 at week 52 and dry retina at week 52) were evaluated using logistic regression (stepwise variable selection).

The patient population evaluated in this *post hoc* analysis includes only those patients with non-missing values for all variables in the model.

Results

Patients

In the VIEW studies, a total of 1815 patients [IVT-AFL 2q4 (n = 613); IVT-AFL 2q8 (n = 607); ranibizumab 0.5q4 (n = 595)] were included in the FAS. Baseline demographics and disease characteristics of participants in the VIEW studies were evenly balanced among all treatment groups (Table 1) (Heier et al. 2012).

Predictors

The following baseline factors were associated with a higher proportion of patients achieving a ≥15 ETDRS letter change from baseline over 52 weeks (n = 1744): younger age [49–69 years; p < 0.0001 (Wald chi-square statistics from the type III analysis of effects)], lower BCVA (10.0–≤45.0 ETDRS letters; p < 0.0001) and smaller CNV size (0.0–≤3.1 DA; p < 0.0001) (Fig. 1A). Conversely, older age (≥90 years; p = 0.0124), larger CNV size (>10.1–≤32.6 DA; p = 0.0002) and predominantly classic CNV (p = 0.0316) at baseline were all associated with a higher proportion of patients losing ≥15 ETDRS letters over 52 weeks (n = 1744) (Fig. 1B); these factors were also associated with any VA loss (≥1 ETDRS letters) at week 52 (n = 1744) (Fig. 2).

With respect to absolute BCVA outcomes, younger age (49–69 years; p = 0.0001), higher baseline BCVA (>64.0–≤83.0 ETDRS letters; p < 0.0001) and smaller CNV size (0.0–≤3.1 DA; p < 0.0001) were all associated with a BCVA ≥20/40 at week 52 (n = 1744) (Fig. 3A), while older age (≥90 years; p < 0.0001), lower baseline BCVA (10.0–≤45.0 ETDRS letters; p < 0.0001), larger CNV size (>10.1–≤32.6 DA; p < 0.0001) and predominantly classic CNV (p = 0.0007) at baseline were all associated with a BCVA ≤20/200 at week 52 (n = 1744) (Fig. 3B).

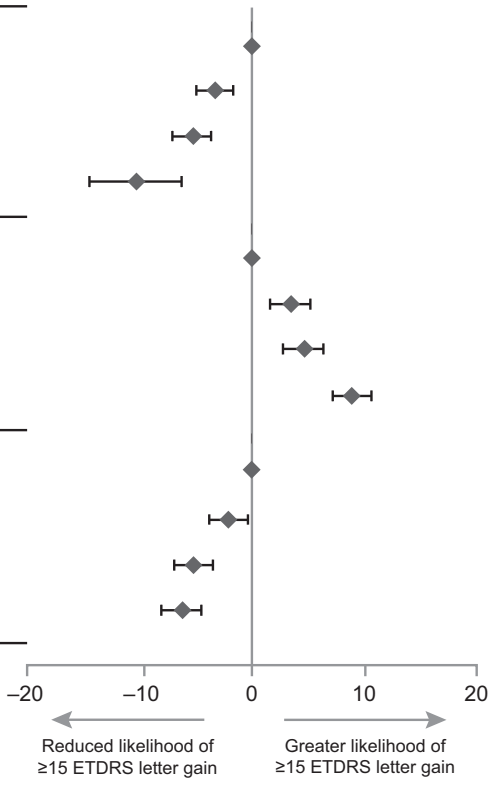
Predictors for the absence of both intraretinal and subretinal fluid (dry retina) at week 52 (n = 1692) included lower BCVA (10.0–≤45.0 ETDRS letters; p = 0.0166), smaller CRT

Table 1. Baseline demographics and patients characteristics.

	VIEW 1				VIEW 2			
	Ranibizumab	Intravitreal Aflibercept			Ranibizumab	Intravitreal Aflibercept		
	0.5q4	2q4	0.5q4	2q8	0.5q4	2q4	0.5q4	2q8
N (full analysis set)	304	304	301	301	291	309	296	306
Age, years (mean ± SD)	78.2 ± 7.6	77.7 ± 7.9	78.4 ± 8.1	77.9 ± 8.4	73.0 ± 9.0	74.1 ± 8.5	74.7 ± 8.6	73.8 ± 8.6
Race, *n* (%)								
White	296 (97.4)	295 (97.0)	291 (96.7)	287 (95.3)	213 (73.2)	226 (73.1)	219 (74.0)	217 (70.9)
Black	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.7)
Asian	0	3 (1.0)	5 (1.7)	4 (1.3)	60 (20.6)	67 (21.7)	61 (20.6)	69 (22.5)
Other	7 (2.3)	5 (1.6)	5 (1.7)	9 (3.0)	17 (5.8)	16 (5.2)	15 (5.1)	18 (15.9)
Sex, *n* (%)								
Men	132 (43.4)	110 (36.2)	134 (44.5)	123 (40.9)	122 (41.9)	133 (43.0)	149 (50.3)	131 (42.8)
Women	172 (56.6)	194 (63.8)	167 (55.5)	178 (59.1)	169 (58.1)	176 (57.0)	147 (49.7)	175 (57.2)
Baseline ETDRS BCVA (mean ± SD)	54.0 ± 13.4	55.2 ± 13.2	55.6 ± 13.1	55.7 ± 12.8	53.8 ± 13.5	52.8 ± 13.9	51.6 ± 14.2	51.6 ± 13.9
Proportion of patients with ≥20/40 BCVA, *n* (%)	4.3 (13)	4.9 (15)	6.3 (19)	6.6 (20)	2.7 (8)	2.6 (8)	5.4 (16)	3.3 (10)
CNV area, mm^2 (mean ± SD)	6.53 ± 5.2	6.59 ± 5.1	6.49 ± 4.5	6.57 ± 5.1	7.59 ± 5.3	8.25 ± 5.8	7.70 ± 5.3	7.75 ± 5.5
Lesion type, *n* (%)								
Predominantly classic	82 (27.0)	87 (28.6)	81 (26.9)	71 (23.6)	70 (24.1)	72 (23.3)	80 (27.0)	88 (28.8)
Minimally classic	101 (33.2)	105 (34.5)	97 (32.2)	110 (36.5)	104 (35.7)	112 (36.2)	103 (34.8)	106 (34.6)
Occult	115 (37.8)	110 (36.2)	121 (40.2)	118 (39.2)	116 (39.9)	123 (39.8)	113 (38.2)	110 (35.9)
Patients with juxtafoveal lesions, *n* (%)	15 (4.9)	13 (14.3)	17 (5.6)	17 (5.6)	20 (6.9)	15 (4.9)	11 (3.7)	14 (4.6)
Lesion size, mm^2 (mean ± SD)	6.99 ± 5.5	6.98 ± 5.4	6.95 ± 4.7	6.89 ± 5.2	8.01 ± 5.7	8.72 ± 6.1	8.17 ± 5.5	8.22 ± 5.9
Central retinal thickness μm (mean ± SD)	315.3 ± 108.3	313.6 ± 103.4	313.2 ± 106.0	324.4 ± 111.2	325.9 ± 110.9	334.6 ± 119.8	326.5 ± 116.5	342.6 ± 124.0
Baseline NEI VFQ-25 scores (mean ± SD)	71.8 ± 17.2	70.4 ± 16.6	71.1 ± 17.8	69.6 ± 16.8	72.9 ± 19.1	70.3 ± 19.4	74.0 ± 18.2	71.3 ± 19.1

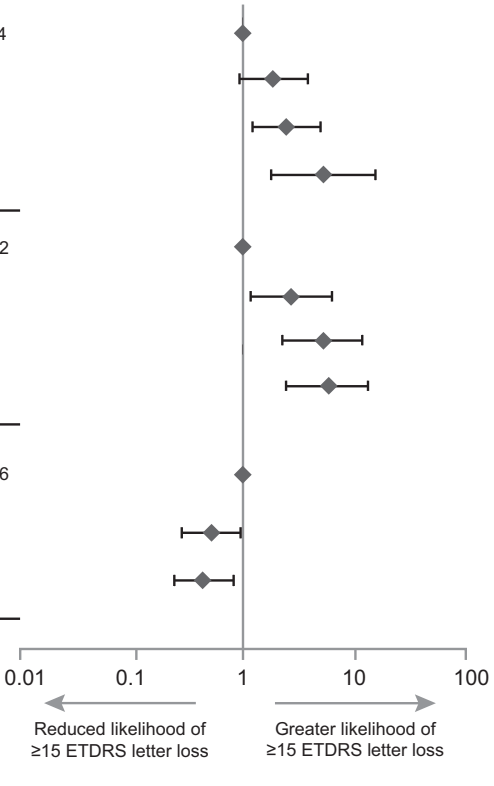
0.5q4, 0.5 mg every 4 weeks; 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; NEI VFQ-25, National Eye Institute 25-item Visual Functioning Questionnaire; SD, standard deviation.

Patient characteristic		N	Estimated difference (95% CI)	Model–specific p value
Age	46–69	388	0	<0.0001
	70–79	711	–3.27 (–4.93 to –1.60)	
	80–89	600	–5.29 (–7.01 to –3.56)	
	≥90	45	–10.38 (–14.53 to – 6.23)	
VA ETDRS score, BL, categorized	>64.0 to ≤83.0	431	0	<0.0001
	>56.0 to ≤64.0	422	3.39 (1.59–5.20)	
	>45.0 to ≤56.0	451	4.58 (2.80–6.36)	
	10.0 to ≤45.0	440	8.91 (7.12–10.71)	
CNV size, BL, categorized	0.0 to ≤3.1	433	0	<0.0001
	>3.1 to ≤6.0	439	–2.08 (–3.87 to – 0.30)	
	>6.0 to ≤10.1	436	–5.20 (–6.99 to – 3.41)	
	>10.1 to ≤32.6	436	–6.29 (–8.08 to – 4.50)	



(A)

Patient characteristic		n/N (%)	OR (95% CI)	p Value
Age	46–69	10/388 (2.6)	1	0.0124
	70–79	37/711 (5.2)	1.884 (0.923–3.846)	
	80–89	39/600 (6.5)	2.455 (1.206–4.999)	
	≥90	6/45 (13.3)	5.297 (1.801–15.584)	
CNV size, BL, categorized	0.0 to ≤3.1	9/433 (2.1)	1	0.0002
	>3.1 to ≤6.0	19/439 (4.3)	2.741 (1.186–6.334)	
	>6.0 to ≤10.1	32/436 (7.3)	5.219 (2.299–11.849)	
	>10.1 to ≤32.6	32/436 (7.3)	5.772 (2.480–13.438)	
CNV type	Predominantly classic	24/452 (5.3)	1	0.0316
	Minimally classic	35/612 (5.7)	0.524 (0.288–0.955)	
	Occult	33/680 (4.9)	0.451 (0.246–0.827)	



(B)

Fig. 1. Predictors for the likelihood of achieving a ≥15 ETDRS letter gain (A) or loss (B) from baseline to week 52 (n = 1744). BL, baseline; CI, confidence interval, CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; n, number of events per patient-year; N, total number of patients; OR, odds ratio; VA, visual acuity.

Patient characteristic		*n*/*N* (%)	OR (95% CI)	p Value
Age	46–69	49/388 (12.6)	1	<0.0001
	70–79	136/711 (19.1)	1.535 (1.074–2.195)	
	80–89	142/600 (23.7)	2.085 (1.457–2.985)	
	≥90	15/45 (33.3)	3.318 (1.645–6.694)	
CNV size, BL, categorized	0.0 to ≤3.1	53/433 (12.2)	1	<0.0001
	>3.1 to ≤6.0	74/439 (16.9)	1.882 (1.250–2.832)	
	>6.0 to ≤10.1	103/436 (23.6)	3.188 (2.107–4.825)	
	>10.1 to ≤32.6	112/436 (25.7)	3.848 (2.514–5.888)	
CNV type	Predominantly classic	95/452 (21.0)	1	<0.0001
	Minimally classic	114/612 (18.6)	0.467 (0.326–0.668)	
	Occult	133/680 (19.6)	0.503 (0.355–0.714)	

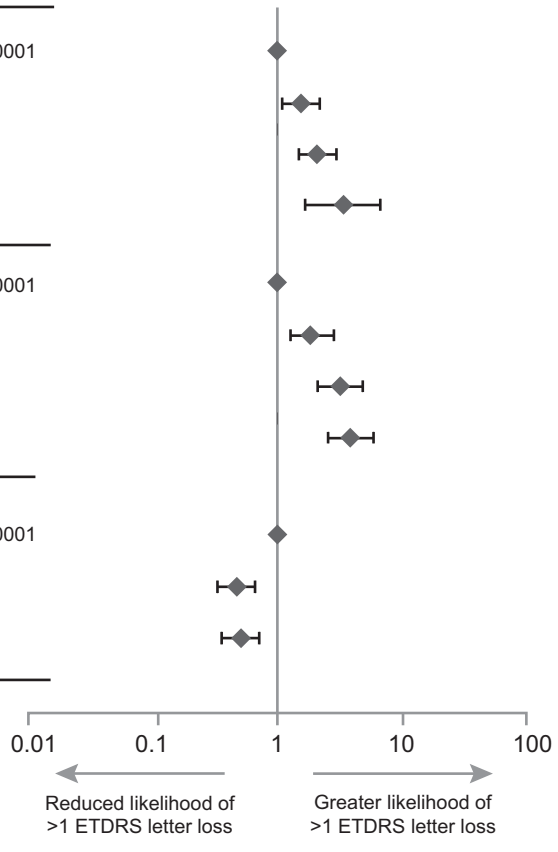


Fig. 2. Predictors for patients losing vision (loss ≥1 ETDRS letters) from baseline to week 52 (n = 1744). BL, baseline; CI, confidence interval, CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; *n*, number of events per patient-year; *N*, total number of patients; OR, odds ratio; VA, visual acuity.

(103.0–≤245.0 μm; p = 0.0190) and treatment group (p < 0.0001) at baseline (Fig. 4). The odds ratios (ORs) of developing a dry retina with IVT-AFL 2q4 or IVT-AFL 2q8 (compared with ranibizumab) were 1.798 (1.388–2.329) and 1.208 (0.942–1.548), respectively (both p < 0.0001).

Race (white/non-white), sex (female/male) and lesion location (subfoveal/juxtafoveal) did not appear to influence the response.

Discussion

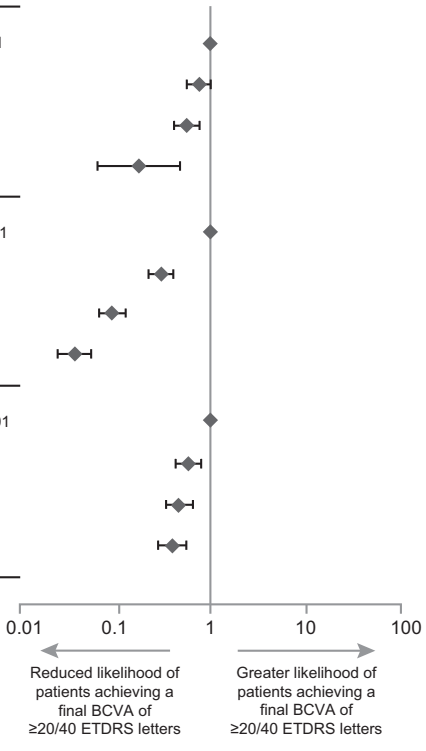
The findings from this exploratory, *post hoc* analysis provide additional insights into possible predictors of visual and anatomical outcomes in patients treated with IVT-AFL or ranibizumab.

Younger age, lower (worse) BCVA score and smaller CNV size at baseline were all associated with improvements in visual gains (higher proportion of patients achieving VA gains ≥15 letters from baseline over 52 weeks). Conversely, those factors associated with greater visual losses (higher proportion of patients losing ≥15 letters from baseline) included older age, larger CNV size and predominantly classic CNV.

For measures based on absolute VA outcomes, younger age, higher (better) BCVA scores and smaller CNV size at baseline were all associated with better visual outcomes (BCVA ≥20/40) at week 52. Worse visual outcomes at week 52 (BCVA ≤20/200) were seen in older patients, as well as those patients with lower (worse) BCVA scores, larger CNV size and predominantly classic CNV at baseline. Due to a possible treatment 'ceiling' effect, it might be expected that patients with lower (worse) BCVA scores at baseline would have greater gains in vision than patients with higher (better) BCVA at the start of treatment. Furthermore, patients with better baseline BCVA have less possibility to gain additional letters than those with worse baseline BCVA; however, these patients are more likely to retain a high BCVA at the end of the treatment period than patients with lower baseline BCVA scores. Because early diagnosis likely captures patients with better starting visions, this latter point argues for the importance of timely/early treatment of the disease.

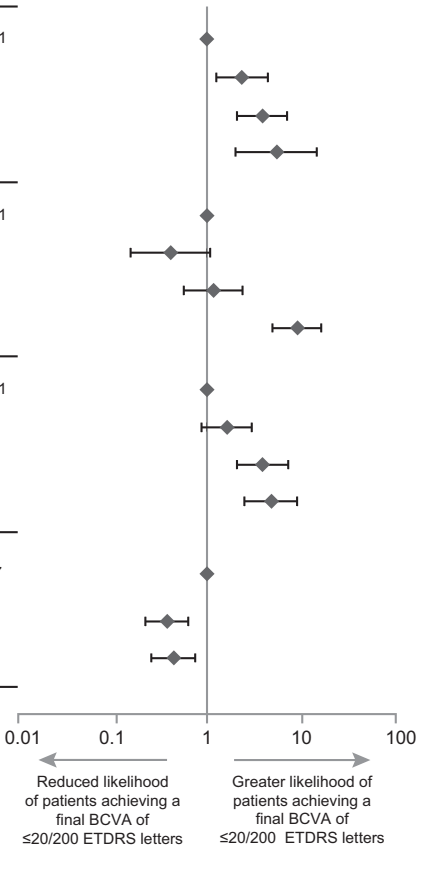
The current study's finding that predominantly classic CNV, when adjusted for baseline VA, is associated with worse visual outcomes (BCVA ≤20/200 and increased probability of a 3-line loss) at week 52 is similar to the finding from CATT (Ying et al. 2013), in which predominantly or minimally classic lesions were associated with worse VA than occult lesions at 1 year. These findings, however, are not as might be expected. Lesions which show classic characteristics are more superficial and theoretically more susceptible to intravitreal therapy than deeper lying occult lesions. However, it may

Patient characteristic		*n*/*N* (%)	OR (95% CI)	p Value
Age	46–69	180/388 (46.4)	1	0.0001
	70–79	267/711 (37.6)	0.756 (0.563–1.016)	
	80–89	177/600 (29.5)	0.569 (0.417–0.777)	
	≥90	6/45 (13.3)	0.176 (0.065–0.480)	
VA ETDRS score, BL, categorized	>64.0 to ≤83.0	310/431 (71.9)	1	<0.0001
	>56.0 to ≤64.0	191/422 (45.3)	0.305 (0.228–0.408)	
	>45.0 to ≤56.0	89/451 (19.7)	0.094 (0.068–0.129)	
	10.0 to ≤45.0	40/440 (9.1)	0.038 (0.025–0.056)	
CNV size, BL, categorized	0.0 to ≤3.1	202/433 (46.7)	1	<0.0001
	>3.1 to ≤6.0	164/439 (37.4)	0.588 (0.427–0.809)	
	>6.0 to ≤10.1	143/436 (32.8)	0.474 (0.342–0.656)	
	>10.1 to ≤32.6	121/436 (27.8)	0.401 (0.288–0.559)	



(A)

Patient characteristic		*n*/*N* (%)	OR (95% CI)	p Value
Age	46–69	14/388 (3.6)	1	<0.0001
	70–79	61/711 (8.6)	2.299 (1.228–4.302)	
	80–89	79/600 (13.2)	3.701 (1.996–6.863)	
	≥90	9/45 (20.0)	5.297 (1.955–14.357)	
VA ETDRS score, BL, categorized	>64.0 to ≤83.0	14/431 (3.2)	1	<0.0001
	>56.0 to ≤64.0	6/422 (1.4)	0.398 (0.150–1.055)	
	>45.0 to ≤56.0	21/451 (4.7)	1.143 (0.563–2.321)	
	10.0 to ≤45.0	122/440 (27.7)	8.736 (4.802–15.891)	
CNV size, BL, categorized	0.0 to ≤3.1	25/433 (5.8)	1	<0.0001
	>3.1 to ≤6.0	29/439 (6.6)	1.590 (0.859–2.944)	
	>6.0 to ≤10.1	48/436 (11.0)	3.764 (2.007–7.059)	
	>10.1 to ≤32.6	61/436 (14.0)	4.617 (2.433–8.760)	
CNV type	Predominantly classic	61/452 (13.5)	1	0.0007
	Minimally classic	51/612 (8.3)	0.372 (0.221–0.629)	
	Occult	51/680 (7.5)	0.430 (0.252–0.733)	



(B)

Fig. 3. Predictors for patients achieving a final BCVA of ≥20/40 (A) and VA ≤20/200 (B) at Week 52 (n = 1744). BL, baseline; CI, confidence interval, CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; n, number of events per patient-year; N, total number of patients; OR, odds ratio; VA, visual acuity.

Patient characteristic		*n*/*N* (%)	OR (95% CI)	p Value
VA ETDRS score, BL, categorized	>64.0 to ≤83.0	303/421 (72.0)	1	0.0166
	>56.0 to ≤64.0	260/413 (63.0)	0.704 (0.523–0.947)	
	>45.0 to ≤56.0	297/437 (68.0)	0.915 (0.677–1.237)	
	10.0 to ≤45.0	301/421 (71.5)	1.113 (0.813–1.522)	
CRT, BL, categorized	103.0 to ≤245.0	302/422 (71.6)	1	0.0190
	>245.0 to ≤304.0	307/431 (71.2)	0.963 (0.712–1.301)	
	>304.0 to ≤383.0	290/423 (68.6)	0.838 (0.620–1.132)	
	>383.0 to ≤868.0	262/416 (63.0)	0.646 (0.477–0.876)	
Actual treatment	R0.5q4	346/550 (62.9)	1	<0.0001
	IVT-AFL 2q4	432/573 (75.4)	1.798 (1.388–2.329)	
	IVT-AFL 2q8	383/569 (67.3)	1.208 (0.942–1.548)	

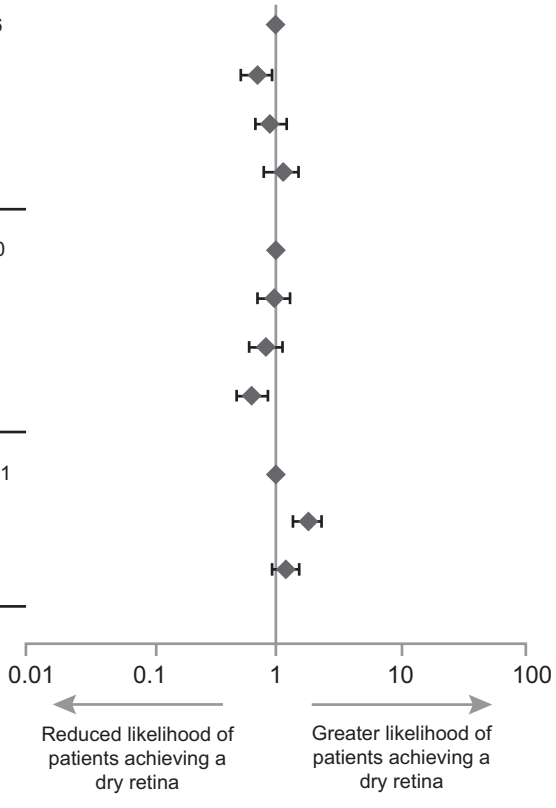


Fig. 4. Predictors for patients achieving a dry retina at week 52 (n = 1692). 2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks; BL, baseline; CI, confidence interval, ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; IRF, intraretinal fluid; IVT-AFL, intravitreal aflibercept; *n*, number of events per patient-year; *N*, total number of patients; OR, odds ratio; R0.5q4, ranibizumab 0.5 mg every 4 weeks.

be that, due to associated haemorrhage, etc., predominantly classic CNV (as an intraretinal, rather than primarily subretinal disease process) is more likely to have a negative effect on VA outcomes in this study population.

These findings, together with those from previously published studies with other anti-VEGF therapies (Boyer et al. 2007; Kaiser et al. 2007; Ying et al. 2013; Finger et al. 2014; Shah et al. 2016), provide sufficient evidence to suggest that there is a strong association between some baseline clinical factors, that is, age, VA and CNV lesion size, and overall visual outcomes following anti-VEGF treatment. As an example, in the 52-week SIGHT study, which compared IVT-AFL 2q8 with photodynamic therapy in Chinese patients (patients switched to IVT-AFL after 28 weeks), the greatest VA benefits were seen in younger patients (aged <65 years) and those with smaller active CNV lesions (< 50% of lesion size) at baseline (Li et al. 2016). Furthermore, in a recent literature review investigating patient response to anti-VEGF therapy in the treatment of nAMD, Tsilimbaris et al. (2016) found that several baseline characteristics were correlated with anti-VEGF treatment response. These included baseline VA, age, lesion size and retinal thickness. Factors such as baseline VA, lesion size and retinal thickness would be expected to be associated with disease duration, suggesting that longer disease duration or lesion chronicity results in worse treatment outcomes. This parameter could not be evaluated in the current analysis, as disease duration before entry into the study was not collected. Nevertheless, these and other findings suggest the need for early treatment to gain optimal treatment outcomes in patients with nAMD.

In comparison with other studies that examined predictors of response to anti-VEGF therapy, the current analysis included an outcome measure related to retinal dryness. Treatment with IVT-AFL 2q4 or 2q8 was associated with a higher chance for a dry retina compared with ranibizumab, with the greatest likelihood associated with the IVT-AFL 2q4 group (odds ratio of 1.798 for the IVT-AFL 2q4 group and 1.208 for the IVT-AFL 2q8 group). In addition to the differences based on treatment assignment, patients in the lowest CRT group (103.0–≤245.0 μm) at baseline were more likely to achieve a dry retina than those in the other CRT groups at baseline.

As with all studies of this nature, ours has a number of strengths and limitations. Strengths include the use of a large patient population [data from two large, rigorously conducted clinical trials (VIEW 1 and 2)] and the ability to directly compare IVT-AFL with ranibizumab. However, limitations include the *post hoc* exploratory nature of this analysis and the lack of statistical correction for multiple comparisons.

In conclusion, based on the findings of this *post hoc*, exploratory analysis,

younger age, lower (worse) baseline BCVA score and smaller CNV size were all associated with better VA outcomes with anti-VEGF therapy over 52 weeks of treatment. Early treatment appears to be beneficial, considering patients with a higher VA and smaller CNV size at the start of treatment were more likely to achieve a BCVA of 20/40 or better at the end of the treatment period. Finally, a higher proportion of patients achieved a dry retina with IVT-AFL 2q4 and 2q8 than with ranibizumab; however, further exploratory studies to evaluate in detail the relationship between a dry retina and visual outcomes will provide additional insights.

Data Access, Responsibility and Analysis

PL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Correspondence:
Paolo Lanzetta, MD
Department of Medicine – Ophthalmology
University of Udine
Piazzale S. Maria della Misericordia
33100 Udine, Italy
Tel: +39 0432 559 905
Fax: +39 0432 559 904
Email: paolo.lanzetta@uniud.it

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