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REVIEW

Predictors of Visual Acuity After Treatment of Neovascular Age-Related Macular Degeneration – Current Perspectives

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Abstract: Visual acuity is a key outcome measure in the treatment of neovascular age-related macular degeneration (nAMD) using anti-vascular endothelial growth factor agents. Large variations in visual responses between individuals within clinical trials and real-world studies may relate to underlying differences in patient and treatment factors. Most notably, a better baseline visual acuity, younger age and smaller choroidal neovascularization lesion size have been strongly associated with achieving better visual outcomes. In addition, there is emerging evidence for other roles including genetic factors and anatomical variables such as fluid status. Apart from patient-related factors, treatments that favor a higher number of injections tend to provide better visual outcomes. Overall, the identification of predictive factors does not currently play an essential role in the clinical management of patients with nAMD. However, they have allowed for the understanding that early detection, timely management and close monitoring of the disease are required to achieve optimal visual outcomes. Further investigation into predictive factors alongside the development of novel therapeutic agents may one day provide a means to accurately predict patient outcomes. Treatment regimens that offer flexible dosing patterns such as the treat-and-extend strategy currently provide a degree of personalization during treatment.

Keywords: age-related macular degeneration, anti-VEGF, visual acuity, demographic, genetic, anatomic

Introduction

Age-related macular degeneration (AMD) is a chronic disease of the eye which is the leading cause of irreversible vision impairment in developed countries.[1] Prevalence rates of AMD for individuals aged between 45 and 85 years range between 7% and 18% across Asian and Western countries.[2] Neovascular age-related macular degeneration (nAMD) or "wet" AMD, is an advanced form of AMD characterized by choroidal neovascularization (CNV), where newly formed blood vessels leak into the retina, causing distortion and rapid loss of vision. nAMD occurs in approximately 10% of individuals with AMD, however it is responsible for up to 90% of vision loss.[2,3] The burden of AMD is expected to increase, as current prevalence rates are estimated to rise by approximately 50% over the next two decades.[2]

While the exact cause of CNV is unconfirmed, it is believed to be triggered by local retinal ischemia/hypoxia, caused by the buildup of abnormal extracellular deposits located between the retinal pigment epithelium (RPE) and Bruch's

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membrane. The overexpression of vascular endothelial growth factor (VEGF) in response to retinal hypoxia has been identified as the main mediator behind the development of CNV.[4–6] These findings have led to a paradigm shift in the treatment of nAMD through the introduction of anti-VEGF medication given intravitreally into the eye. Anti-VEGF agents primarily target and block VEGF-A isoforms, preventing further vision loss caused by angiogenesis, fluid leakage and subsequent scar formation. The improvement and stabilization of vision through fluid reduction is the primary goal of treatment, which also improves vision-related quality of life.[7] As a result, visual acuity (VA) has been considered one of the primary markers for treatment success within several pivotal Phase 3 clinical trials; namely the MARINA[8] and ANCHOR[9] trials for ranibizumab (Lucentis; Genentech, South San Francisco, California), the VIEW1 & VIEW2 studies[10,11] for aflibercept (Eylea; Regeneron, Tarrytown, New York) and more recently in the HAWK and HARRIER trials[12] for brolucizumab (Beovu; Novartis, Basel, Switzerland). In addition to these agents which have been FDA approved for ocular use, bevacizumab (Avastin; Regeneron) has been used off-label, and its non-inferiority to ranibizumab has been demonstrated in the CATT studies.[13,14] In each of their landmark studies, over 90% of patients maintained VA levels within 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters over the course of treatment. Remarkably also, 30–40% of patients demonstrated visual improvements beyond the 15 letter threshold, demonstrating superiority over previously used photodynamic therapy and laser photocoagulation treatment, which rarely saw VA improvement.[15,16]

However, while the introduction of anti-VEGF therapy has been revolutionary in reducing rates of legal blindness associated with AMD,[17] not all patients respond positively, with a small remainder of patients (~5–10%) experiencing significant reductions in vision. These variations are also seen in the real world, with post-marketing trials and clinical studies finding larger proportions of patients who lose vision compared to the control trials.[18–20] In addition to these early responses, further treatment variation occurs in the longer term past the first 1–2 years of treatment, with some patients experiencing gradual declines in visual acuity despite continuous intensive treatment and a good initial response.[21–23]

It currently remains unclear as to why such heterogeneity in treatment response exists. Though several retrospective analyses have identified several functional, demographic, genetic and anatomic factors associated with various visual outcomes. The identification of prognostic factors allows the provision of personalized medicine, as physicians can provide patients with a more accurate expectation for their visual prognosis. This review investigates factors which may have a predictive value in determining visual response after anti-VEGF treatment among patients with nAMD and assesses the current roles of predictive markers in treatment decision-making.

Literature Search Method

Articles up until January 2021 were initially searched using PubMed by 2 independent authors (LP & GB) using a combination of the terms “Macular degeneration”, “Neovascular”, “Predictive factors”, “Predictors”, “Visual acuity” and “Visual outcomes”. From 190 identified articles, 101 non-relevant articles and 9 non-English articles were excluded after screening through abstracts. The remaining articles were reviewed to generate a list of relevant predictors for further investigation. Sixty-two further studies were identified following manual searching of secondary analyses from major randomized clinical trials of anti-VEGF and separate searches that included additional terms specific for sub-categories of predictors including “smoking”, “pharmacogenetics”, “polymorphisms”, “CFH”, “ARMS2”, “HTRA1”, “VEGF-A”, “VEGFR-2”, “GWAS”, “Optical coherence tomography”, “Atrophy” and “Hemorrhage”. There was a focus on post-hoc analyses of clinical trials and large retrospective studies which used multivariate analysis. Smaller studies or those which used univariate analyses were also included if they demonstrated a significant novel finding. This excluded 48 articles, leaving 94 studies which were included in this review.

Variations in Outcome Reporting and Risk Factor Analyses

Different measures of efficacy have been used throughout the literature. Most studies report visual outcomes as a continuous variable either in terms of visual gain (either in ETDRS letters or using a logMAR equivalent), or as absolute levels of VA achieved by the end of the observational period. On the other hand, outcomes have also been evaluated categorically, through the grouping of participants via their visual response. Though the thresholds for these categories vary between studies, a loss of ≥15 letters

for poor responders has been the most popular definition. Alongside these variations in outcome measures, there have been differences in study designs and statistical analyses and reporting of the various risk factors within the literature. As such meta-analyses have not been previously possible[24,25] and will not be attempted in this exploration for the same reason.

Functional Variables

Visual Acuity

Baseline VA has been the most thoroughly investigated variable and its relationship with visual response following treatment has been well established as the most significant predictor of visual outcome in both clinical trials (Table 1) and real-world studies (Table 2).

VA changes following treatment are heavily influenced by ceiling effects, where patients with better VA at presentation have a reduced capacity or "ceiling" for VA gains compared to those who present with lower baseline VA levels. Post-hoc analysis of the MARINA study found a 1.2–1.6 letter reduction in VA gains for every 5-letter increase in baseline VA.[26] Meanwhile in the VIEW studies, VA gains were +0.65 letters higher for every 1 letter reduction in baseline VA.[27] However, the presence of intraretinal fluid (IRF) at baseline reduced the expected letter gain to +0.22.[27]

While it appears that anti-VEGF treatment is more effective in eyes with poorer VA, patients presenting with better initial VA are more likely to have better final VA. A large retrospective analysis from the Moorfields Eye Hospital (MEH) database reported a 43% increase in likelihood for achieving and maintaining a VA of 20/40 for every 5-letter increase in VA at baseline.[28] Meanwhile, data from the Swedish Macular Register revealed that eyes with initial VA >60 letters (20/63) had only a 20% risk of having low VA (≤60 letters) after 1 or 2 years of treatment, compared to 60% in eyes with low initial VA.[29] This relationship has also been observed in several long-term studies,[30–35] suggesting that the larger visual gains in those with worse initial VA are not enough to overcome a good starting VA despite continuous treatment. As those with worse initial VA are also more likely to respond negatively to treatment, low baseline VA may be an indicator for worse disease severity as there may be underlying pathology not treatable by anti-VEGF, such as atrophy, scarring or other anatomical changes not controlled for in multivariate analysis. van Asten et al,[36] found that those with worse baseline VA were more likely to be non-responders (defined by loss of more than 30% initial letters) after the first 3 months of treatment (OR: 3.3, VA 20/63-20/200 vs >20/63). Similarly, analysis of data from the Fight Retinal Blindness! (FRB) registry found that eyes with VA better than 20/40 were 39% less likely to experience a ≥30 letter loss than those with worse baseline VA after 5 years of treatment.[37]

Although baseline VA is consistently associated with visual outcomes, one's early response may be a better predictor of their visual trajectory.[38–40] The CATT studies found that an individual's VA gain at week 12 of treatment was a stronger predictor of their long-term visual gains than the combination of all their significant baseline predictors including initial VA (R^2 for 2 year VA gains: 0.30 vs 0.13).[40] Similar findings have also been found from the FRB registry,[39] where those who achieved good vision (≥70 letters) by their 4th injection were more likely to maintain good vision after 3 years of treatment than those who did not (OR: 9.8, VA ≥70 vs <70 letters).

As anti-VEGF therapy does not cure nAMD, the nature of the relationship between presenting VA and its response to treatment suggests that individuals should be treated earlier in the disease course. Studies which find that a shorter duration between symptom occurrence and treatment initiation is also associated with better visual outcomes support this notion.[41–44]

Patient Characteristics

Age

Similar to VA, strong relationships between age and visual outcomes were identified in the early clinical studies, with less VA gain seen in older patients (Table 1).[26,40,45–47] In the MARINA study,[26] a 13.6 year difference in age at disease diagnosis was associated a 5-letter reduction in VA gains in the older patient. Meanwhile in the ANCHOR study,[45] an 18.8 year difference in age was associated with a 5-letter reduction in VA gain. In the HARBOR study,[48] patients aged ≤73 years at baseline gained 4.5 letters more than those aged >73 after ranibizumab treatment. The VIEW studies found that older age was also associated with negative treatment outcomes, with older patients more likely to lose VA over their first year of aflibercept treatment (OR for >1 letter loss: 2.1, ages 80–89 vs 46–69 years).[47] Over the first 2 years of CATT,[40,46] older age was associated with less VA gains, worse final VA levels and a decreased likelihood for a ≥15

Table 1 Summary of Clinical Trials Investigating Predictors of Visual Outcomes in Anti-VEGF Treated Patients

Study	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
ANCHOR[45]	RBZ 0.3/0.5mg, q1m or PDT prn	1	• RBZ treated arms gained more VA than the PDT group • Lower baseline VA, smaller baseline CNV lesion size and younger age associated with better VA gains	• Gender • CNV type • Duration between diagnosis and treatment
MARINA[26]	RBZ 0.3/0.5mg vs sham	2	• Lower baseline VA, smaller baseline CNV lesion size and younger age associated with better VA gains	• Gender • CNV type • Duration between diagnosis and treatment
MARINA & ANCHOR[122]	RBZ	1	• Fellow eye visual acuity was not predictive of study eye response	• Fellow eye visual acuity
PrONTO[123]	RBZ prn	2	• Larger reductions in CRT after 1 month associated with better VA gains	• # of injections
PIER[124]	RBZ 0.3/0.5mg q3m	2	• Lesion inactivity determined by FFA at 3 months associated with better 1 year VA gains • Lesion inactivity on determined by OCT at 5 or 8 months associated with better 2 year VA gains	• RBZ dose
CATT[46,67]	RBZ or BVZ, prn or q1m	1	• Factors associated with worse final VA were older age, worse baseline VA, larger CNV size, predominantly or minimally classic lesions, presence of GA, thicker foveal thickness and the presence of RPE elevation • Factors associated with less VA gains were older age, better baseline VA (≥20/40), larger CNV size, absence of RAP lesions and presence of RPE elevation • Factors associated with a decreased likelihood of VA gains ≥15 letters were better baseline VA, worse VA in the fellow eye, larger CNV size, absence of RAP lesions, thinner foveal thickness and the presence of RPE elevation • PRN treatment group was less likely to gain ≥15 letters compared to fixed monthly dosing	• SNPs of CFH, ARMS2, HTRA1 & C3 • No interactions between treatment groups and predictors
CATT[40,106]	RBZ or BVZ, prn or q1m	2	• Older age, baseline VA of 20/40 or better, larger CNV area, presence of GA in the study eye, thicker (≥425 μm) or thinner (≤325 μm) CRT, and presence of RPE elevation were associated with less VA gain • VA gains at 12 months (R^2=0.30) more predictive of 2 year VA gains than baseline VA (R^2=0.13) • Baseline non-foveal GA (OR: 2.86), larger CNV area (OR: 3.91, 4 DA vs ≤1 DA), and BVZ treatment (OR: 1.83) were associated with a VA loss of 15 or more letters by weeks 88 and 104 • Scars, GA, persistent IRF and SRHM were more common in eyes with VA loss	• Treatment group • # of treatments or visits
CATT[49]	RBZ or BVZ, prn or q1m	5	• Better baseline VA associated with better final VA but less VA gains • Smaller CNV lesion size presence of SRF associated with better final VA and better VA gains • Absence of RPE elevation (OR: 3.85), female gender (OR: 1.79) and BVZ use during first 2 years of treatment (OR: 1.62) more likely to gain ≥3 lines • Current (OR: 2.61) and former smokers (OR: 1.21) more likely to have final VA 20/200 or worse	• Various SNPs • Hypertension, diabetes • Treatment group • IRF • Various RT measures
HARBOR[48]	RBZ 0.5/2mg, prn or q1m	1	• Baseline predictors of better VA gains and/or percentage of 3-line gainers included lower VA, younger age, smaller CNV leakage area, smaller area of occult CNV, and presence of SRF • Baseline predictors of final VA better than 20/40 included higher VA, smaller CNV leakage area, and presence of SRF	• Gender, ethnicity, smoking status • Treatment regimen • CNV type • Other baseline morphologies

(*Continued*)

Table 1 (Continued).

Study	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
HARBOR[125,126]	RBZ 0.5/2mg, prn or q1m	2	• Those in the lowest quartile for BCVA-LLVA gap at baseline (≤ 17 letters) gained more VA than those in the highest quartile (≥ 33 letters) and were more likely to gain ≥ 15 letters as well as lose ≥15 letters • Patients who achieved peak BCVA after 6 months of treatment, had better VA gains and final VA than those who peaked during the first 6 months	• Treatment group • Baseline morphology
VIEW[47,97]	RBZ q4w, AFL q4w/q8w	1	• Younger age, lower VA and smaller CNV size more likely to have ≥15 letter VA gains • Older age, larger CNV size and pre-dominantly classic CNV lesions likely to lose ≥1 and ≥15 letter VA • Younger age, better baseline VA and smaller CNV size more likely to have final VA better than 20/40 • Older age, lower baseline VA, larger CNV size and predominantly classic CNV lesions more likely to have final VA worse than 20/200 • Higher baseline VA associated with less VA gain (−0.25 letters per letter increase) • IRF and PED at baseline associated with less VA gains (−2.77 and −1.88 letters respectively) • SRF at baseline associated with better VA gains (+2.11 letters)	• Gender • Ethnicity • Lesion location
EXCITE[99]	RBZ 0.3mg q1m or 0.3/0.5mg q3m	1	• Baseline IRF and infrequent treatment associated with less VA gains (−3.6 and −4.4 letters respectively) • PVD and SRF at baseline associated with better VA gains (+3.5 and +2.8 letters respectively) • Interaction between SRF, PVD and treatment frequency, where those without SRF and/or PVD at baseline requiring frequent dosing for better VA gains	• CRT, PED • RBZ dose
OSPREY[102]	Brolucizumab or AFL	1	• Decreased SHRM correlated with better VA gains • Improved ellipsoid zone integrity was associated with better VA gains	• Sub RPE volume
AREDS[111]	Any anti-VEGF	2	• Patients with final VA of 20/200 or worse were more likely to be non-White, have lower baseline VA, have macular atrophy or macular hemorrhage at baseline and fewer anti-VEGF injections in total	-

Abbreviations: AFL, aflibercept; RBZ, ranibizumab; BVZ, bevacizumab; PRN, pro re nata; VA, visual acuity; BCVA, best-corrected visual acuity; LLVA, low-luminance visual acuity; PDT, photodynamic therapy; CNV, choroidal neovascularization; RT, retinal thickness CRT, central retinal thickness; FFA, fundus fluorescein angiography; OCT, optical coherence tomography; GA, geographic atrophy; RPE, retinal pigment epithelium; RAP, retinal anomalous proliferation; SNP, single nucleotide polymorphism; IRF, intraretinal fluid; SRF, subretinal fluid; SHRM, subretinal hyper-reflective material; PED, pigment epithelial detachment; PVD, posterior vitreous detachment.

letter VA increases, however this was no longer significant at the 5-year follow-up[49] suggesting that age does not influence long-term outcomes. In real world studies, the relationship between age and visual outcome is not as consistent (Table 2). Though associations are found in larger observational cohorts,[28,29,50] suggesting this is due to smaller sample sizes and larger patient variations in combination with its relatively small effect size.

The effect of age may be influenced by other factors, with Yamashiro et al.[51] finding that age was associated with 12-month VA changes in typical nAMD patients, but not for those presenting with the polypoidal choroidal vasculopathy (PCV) variant of AMD. As age is a major risk factor for advanced AMD, its relationship with visual outcomes likely represents part of the natural history of the disease. These individuals should be considered more carefully during treatment.

Gender

There have been some associations between prevalent AMD and gender which may suggest that the course of treatment may differ between men and women.[52] However, despite gender being regularly included in risk factor analyses in clinical trials and retrospective studies, no significant associations have been found between gender and the visual response to anti-VEGF treatment in

Table 2 Summary from Major Real-World Studies Investigating Predictors of Visual Outcomes in Anti-VEGF Treated Patients

Author (Year)	Study	N (Eyes)	Treatment	Duration (Years)	Findings and Significant Factors	Non-Significant Factors
Holz (2016)[50]	AURA	1184	RBZ	2	• Higher baseline VA (−0.42 per letter) and older age (−0.28 per year) associated with less VA gains • Higher # of ophthalmoscopies and OCT's (+0.13 per observation) and higher total injections (+0.32 per injection) associated with better VA gains • Age, baseline VA and # of ophthalmoscopies and OCT associated with VA maintenance (<15 letters) • Age, baseline VA and # of injections associated with ≥15 letter gains	-
Fasler (2019)[118]	MEH	3357	AFL or RBZ	2	• Younger age, lower baseline VA and more injections were associated with higher VA gains	• Gender
Nguyen V (2019)[39]	FRB	2051	Any anti-VEGF	3	• Eyes with VA >70 letters by the 4th injection were more likely to have final VA >70 letters (OR: 9.8) • VA change at 4th injection correlated more strongly with final VA (R^2=0.37) than baseline VA (R^2=0.20)	-
Nguyen CL (2019)[37]	FRB	856	Any anti-VEGF	5	• Older age (OR: 1.33, >80 vs ≤80 years), lower total number of injections (OR: 0.97 per injection) and a higher proportion of visits with active CNV (OR: 1.97 upper vs lower quartile) were associated with sustained ≥15 letter VA loss • Older age (OR: 1.64, >80 vs ≤80 years), lower baseline VA (OR: 1.64, ≤70 vs > 70 letters), lower total number of injections (OR: 0.96 per injection) and a higher proportion of visits with active CNV (OR: 2.22 upper vs lower quartile) were associated with sustained ≥30 letter VA loss • Eyes with sustained VA loss were more likely to have haemorrhage, RPE tears, GA and subretinal fibrosis	• Lesion type • GLD
Fu (2020)[28]	MEH	7802	AFL or RBZ	~19 months	• Better baseline VA associated with an increased likelihood of achieving 20/40 (HR: 1.43 per 5 letters) • Higher # of injections associated with an increased likelihood of achieving 20/40 (HR: 1.12 per injection) • Older patients were less likely to achieve 20/40 (HR: 0.88 per 5 years) • Baseline VA, injection # and age also associated with the ability to maintain 20/40 or better • Those who had an incomplete loading phase less likely to achieve 20/40 (HR: 0.87) and more likely to have final VA 20/400 or worse • Those on RBZ more likely to have final VA 20/400 or worse	• Drug choice (for good visual outcomes) • Sex • Ethnicity
Ho (2020)[32]	IRIS	162,902	Any anti-VEGF	2	• Eyes with worse baseline VA had larger VA gains but worse final VA	-
Schroeder (2020)[127]	SMR	6142	Any anti-VEGF	2	• Those with worse baseline VA, worse-seeing eye treated, older age, larger CNV lesion size at baseline and treated by RBZ or BVZ monotherapy were more likely to have final VA of ≤ 35 letters	• Sex • Lesion type and location • Symptom duration

Abbreviations: AFL, aflibercept; RBZ, ranibizumab; BVZ, bevacizumab; VEGF, vascular endothelial growth factor; CNV, choroidal neovascularization; OCT, optical coherence tomography; GLD, greatest linear dimension; RPE, retinal pigment epithelium; GA, geographic atrophy; VA, visual acuity.

AMD, except in the 5 year follow-up of the CATT study,[49] where females were more likely to ≥15 letter VA gains than males (OR: 1.79).

Ethnicity

The influence of ethnicity is inconclusive as few studies have been performed in diverse populations, however most large studies have found no direct relationship between ethnicity and visual outcome.[28,48] Outcomes related to ethnic background may be tied to CNV lesion sub-type due to the higher prevalence of PCV seen within Black and Asian populations compared to Caucasian populations.[53–55] PCV has been found to be associated with poor anatomic responses to ranibizumab treatment[54,56] and is likely to result in worse visual outcomes in the longer term. Differences in genetic susceptibilities may underlie ethnic differences in treatment outcomes.

Systemic Disease and Social Habits

There are several well-known systemic diseases and behavioral risk factors for AMD such as cardiovascular disease, smoking and nutrition.[57] van Asten et al[36] found that patients with a history of diabetes mellitus were 2.1x more likely to have a non-response to treatment, however no associations were found for cardiovascular disease, smoking status or body mass index. Piermarocchi et al.[58] reported that those with hypertension as well as current and former smokers gained less VA (−3.86 and −4 letters respectively) over 1 year of ranibizumab treatment. Similarly, Lee et al.[59] found that current smokers were more likely have poor VA improvement (VA gain below group median) after ranibizumab treatment (OR: 7.5). Meanwhile, the 5-year follow-up of CATT found that those who were current smokers at baseline were more likely to have worse final VA (OR for VA <20/200: 2.61),[49] suggesting that smoking may exert long-term detrimental effects on VA. In contrast to these findings, a larger majority of studies have failed to find associations.[48,60–66] However, while their role in determining treatment response is unclear, these risk factors remain as strong modifiable risk factors for disease prevention and the improvement of general health.

Genetics

Like other patient factors, genetic polymorphisms that have been strongly associated with the development of nAMD have also been investigated for their role in determining treatment response. Initial investigations were done into AMD risk alleles such as single nucleotide polymorphisms (SNPs) involving the CFH & ARMS2 genes. Analysis of data from the CATT clinical trials was unable to find any associations between SNPs of CFH, ARMS2, HTRA1 and C3 with treatment response across drugs or dosing regimens.[67] Similar results were obtained from analyzing data from the IVAN trials,[68] which also could not find associations in SNPs of CFH, FZD4, ARMS2 and HTRA1. However for the CFH gene, two meta-analyses which have included the CATT and IVAN studies,[69,70] have confirmed that the Y402H polymorphism of CFH was in fact associated with treatment response, with those carrying the minor allele having reduced VA gains. This may be linked to ethnic variations, with subgroup analyses in both papers finding the relationship occurring in Caucasian populations and not East Asians, however it may be due to the significantly lower incidence rates of CFH polymorphisms in Asians and the limited number of Asian studies included. On the other hand, two meta-analyses of studies investigating polymorphisms of ARMS2 have found that the minor allele of A69S was associated better treatment responses to anti-VEGF among East Asians;[71,72] though not all studies included used visual acuity to define treatment response. For HTRA1 gene, a meta-analysis of five studies found no associations between its polymorphisms and treatment response.[73]

Attention has also turned to investigate SNPS involving VEGF, such as VEGF-A & VEGFR2/KDR polymorphisms. However, there have been many conflicting results with large studies failing to find associations.[74,75] For VEGF-A, Lazzeri et al[76] found that SNP rs699947 was related to an early visual response following 3 months of RBZ treatment, with patients carrying the minor allele experiencing positive VA gains (+6.3–7.4 letters) compared to those without, who lost VA following treatment (−1.8 letters). However, Park et al[77] and Cruz-Gonzalez et al78 have both found that the minor allele of rs699947 to be associated with worse visual outcomes after 5 and 12 months respectively. Individuals carrying the minor allele of rs833061 were also more likely to gain VA (≥5 letters) after 1 year of RBZ treatment (OR: 1.62).[78] For VEGFR-2, Hermann et al64 found that SNPs rs4576072 and rs6828477 were independent predictors for VA gains, with carriers of three minor alleles experiencing positive VA gains (~13 letters) compared to those without any minor alleles after 1 year of RBZ treatment. However, the larger CATT and IVAN studies failed to find

associations between SNPS of VEGF-A and VEGFR-2 and VA response.[74,79]

In 2017, 8 polymorphisms of VEGF-A (rs699947, rs699946, rs833069, rs833061, rs2146323, rs1413711, rs2010963 and rs1570360) and 1 polymorphism of VEGFR-2 (rs2071559) were investigated by Wu et al,[80] in a meta-analysis of 8 studies, which found anti-VEGF treatment to be more effective in patients homozygous for the minor allele of VEGF-A rs833061. While this meta-analysis also included studies which assessed anatomic outcomes, sub-analysis of studies describing purely visual outcomes found stronger associations, with OR's for a positive visual response ranging from 2.6 to 3.8 across the genotypic models.

VEGF isoform and receptor polymorphisms have the potential to result in differences in treatment responses between anti-VEGF medications, as aflibercept has additional binding capabilities to PGF and VEGF-B compared to bevacizumab and ranibizumab which only target isoforms of VEGF-A. A Phase 4 trial of aflibercept[81] found strong associations with polymorphisms of VEGF-B (rs12366035) and C5 (rs25681), with those homozygous for their minor alleles more likely to have ≥15 letter gains (OR: 217 and 19.7, respectively). Smaller associations were also found for polymorphisms within CX3CR1, CETP, IL6 and CCL2. These results are promising as it suggests that responses to different anti-VEGF agents may be tied to separate gene polymorphisms.

Apart from selected targeted studies, broader approaches using genome-wide association studies have the allowed identification of other candidate genes associated with treatment response such as CTGF,[82] OR52B4,[83] and CCT3,[84] however a lack of association with previously investigated genes have also raised further uncertainty.

While the role of pharmacogenomics is promising, the prevalence of predictive genes must be common enough and their effects must be strong enough to warrant routine genetic testing in a clinical setting. Despite the availability of several meta-analyses, more individual studies are required in order to further investigate the effects of less commonly assessed SNPs, treatment-related effects and ethnic contributions. Furthermore, external clinical validation of the effects of identified SNPs are required through prospective trials to confirm their roles.

Anatomic Factors

Given the expanded role of imaging in the diagnosis and management of nAMD, considerable efforts have been made to identify potential anatomic characteristics that may predict visual outcomes. Although initially predominantly examination or angiographically based, the expanded role of OCT has meant that many of these factors are now predominantly assessed via OCT imaging. Broadly speaking, factors can be predictive from baseline or during treatment, and both are discussed below.

Lesion Type and Lesion Size

In terms of VA gains, no significant difference has been found between the responsiveness of classic or occult lesions to anti-VEGF agents in large RCTs (Table 1). However, CATT did show that those with classic lesions had lower final VA at 1 year compared to occult lesions (64.2 vs 70.4 letters) yet were more likely to gain ≥15 letters on univariate analysis,[46] and VIEW 1/2 showed that those with classic lesions were more likely to have a final VA worse than 20/200 at 1 year but were more likely to lose ≥15 letters instead.[47] Since those with classic lesions more commonly present with worse VA in these studies, we would expect this to translate into better overall VA gains due to the effects of baseline VA. However, the lack of differences suggests that apart from a small group of good responders, those with classic lesions perform relatively worse compared to other subtypes.

Retinal Angiomatous Proliferation (RAP) lesions have also been associated with increased VA gains after anti-VEGF therapy compared to other lesion types in both the CATT and VIEW trials.[79] These benefits are most pronounced early in therapy (during the 1st year), with differences in visual outcomes between RAP lesions and other angiographic lesion types becoming non-significant after 2 years of therapy.[85] However, RAP lesions have also been linked to higher rates of geographic atrophy (GA), notably in the CATT study,[85] and it remains to be seen if this has any effect on RAP lesions as a predictor of vision with even longer follow-up times, given the role of atrophy in long-term visual decline, as discussed below.

Larger baseline lesion size has been consistently associated with worse VA gain in multiple large RCT's, including the MARINA,[26] ANCHOR,[86] CATT[46,87] and VIEW studies.[88] In the CATT, compared to those with a lesion size ≤2.54 mm^2, patients with a lesion size >10.2 mm^2 experienced less VA gain (+4.2 vs +8.7 letters), had a lower

proportion of ≥15 letter gainers (23.8% vs 30.1%) and had worse final VA (64.5 vs 69.9 letters) after 1 year of treatment.[46]

Retinal Thickness

OCT measured retinal thickness (RT) is a commonly assessed clinical trial outcome and has been used as a criteria for treatment in some trials including HAWK/HARRIER,[89] and it is important to determine in each instance what is meant by retinal RT. Frequently used terms such as central retinal thickness (CRT) or central macular thickness (CMT) in some publications may also include subretinal fluid (SRF) in this measurement, and in some case also include pigment epithelial detachment (PED) height, although here we refer to thickness of the retina alone, excluding SRF or PED. In the CATT, thinner (<120μm, 57.7 letters) or thicker (>212, 64.0 letters) retinal thickness (not including SRF or PED) had worse final VA than those between those two ranges (12–212μm, 72.0 letters) after 2 years of therapy.[90] Similarly, the PrONTO study also found a correlation between change in RT and VA change at 3 and 12 months,[91] suggesting improved retinal thickness is a predictor of greater VA gain.

There is also recent evidence that fluctuations in RT may be a poor prognostic factor. Retrospective analysis of pooled data from the CATT and IVAN trials showed that greater fluctuations in RT were associated with worse VA gains after 2 years, with individuals in the highest quartile for RT variations experiencing and average of 6.27 less letter gain than those who had the least variation in RT (95% CI: −8.45 to −4.0). Individuals with higher variations in RT were also more likely to develop fibrosis and/or GA.[92]

Retinal Exudation – Intraretinal Fluid (IRF), Subretinal Fluid (SRF) and Subretinal Hyperreflective Material (SHRM)

Both IRF and SRF have been studied extensively as markers of disease activity. The presence of IRF has been demonstrated to be associated with worse vision both at baseline and during treatment in large clinical trials including both CATT and VIEW,[27,90] as well as at baseline in the EXCITE study.[93] In VIEW,[44] those with IRF gained 3.85 less letters after 1 year of aflibercept treatment. Recent analysis has also suggested that the volume of IRF is of importance, with increased IRF volume associated with progressively worse BCVA change in post-hoc analysis of the HARBOR trial,[94] as well as in post-hoc analysis of the FLUID trial.[95] Location of IRF was also important in the FLUID analysis, with IRF in the central 1mm significantly associated with reduced VA gain, but IRF in the surrounding 1–6mm not associated with VA change.[95]

The role of SRF, in contrast, is less clear. Analysis of CATT, VIEW and HARBOR has shown that SRF at baseline may be predictive of better visual outcomes,[48,90,94,96,97] and that residual SRF may be associated with larger VA improvement at 24 months in the HARBOR trial. Both the EXCITE and FLUID trials have shown that individuals with SRF could tolerate extended treatment intervals without adversely affecting visual outcomes.[98,99] However, post-hoc analysis of the FLUID trial has shown that increasing SRF volume within the central 1–6mm (but not the central 1mm) of the retina is associated with increasingly reduced VA (−0.2 letters per 100nL).[95] Similarly, post-hoc analysis of the HAWK and HARRIER trials showed that eyes with greater SRF volume at the end of dose loading (12 weeks) had lower VA gain from weeks 12 to 96 than those with lower SRF volume, suggesting that the effect of SRF as a prognostic factor may in part be dependent on the volume of SRF present.[100]

SHRM is an OCT-detectable form of exudation that manifests as hyperreflectivity between the RPE and the retina. The presence of SHRM, particularly at the foveal center, has been associated with significantly worse VA in the CATT study at year 2 (73.5 vs 63.9 letters),[101] as well as being a predictor of poor final VA at year 5.[87] Decreased SHRM volume correlated with improved vision in post-hoc sub-analysis of the OSPREY trial,[102] suggesting that SHRM is an important marker of outcomes in neovascular AMD.

The effect of changes in retinal exudation volume highlights the importance of ongoing monitoring and comparison of retinal imaging across the course of nAMD treatment, as worsening of exudation volumes may result in worse visual outcomes. This may require alterations to management to more effectively control.

Pigment Epithelial Detachments

The presence of PED has been associated with worse baseline vision in nAMD, as well as reduced VA gain in some series such as the CATT study,[46] although this was not seen in the HARBOR study.[103] Response of a PED to therapy has not been associated with visual outcomes in multiple studies,

including retrospective analysis of the HARBOR and VIEW trials,[97,103,104] although post-hoc analysis of the VIEW study showed that patients with a PED at baseline who developed IRF during follow up had the lowest VA gains of any combination of anatomic parameters.[27]

Based on these findings, treatment aimed at eliminating or reducing the size of a PED is currently not recommended,[105] although ongoing monitoring and treatment of any signs of retinal exudation, particularly IRF, is encouraged, given the poorer prognosis of IRF in combination with PED.

RPE Atrophy

Long-term follow-up of a number of clinical trial cohorts has shown that atrophy development is a major cause of long-term visual decline. Five-year outcomes of the CATT cohort showed that the development of atrophy was a significant reason for visual decline in this cohort (mean final VA 62 letters for no foveal pathology vs 53 for GA),[87] and foveal GA at year 2 was associated with worse vision at year 5. The presence of nonfoveal GA at baseline was a risk factor for visual acuity loss at 2 years in the CATT,[106] suggesting that GA progression is an important reason for vision loss even during the first few years of anti-VEGF therapy. Similarly, post-hoc analysis of the subset of the Age-Related Eye Diseases Study 2 (AREDS2) cohort who had neovascular AMD identified atrophy as being the cause of 60% of cases of poor vision (<20/200).[106] Pooled analysis of the ANCHOR, MARINA and HORZION studies also showed that macular atrophy progression was the major cause of visual decline 7 years after commencing treatment,[107] implying that increasing central atrophy is a poor prognostic factor.

Hemorrhage and Subretinal Fibrosis

The presence of clinical hemorrhage by itself has not been associated with worse visual outcomes, with the CATT study showing that lesions composed of >50% hemorrhage had similar VA gains at 2 years compared to those that were not.[108] Hemorrhage, however, needs to be clearly defined, as the presence of sub-retinal hemorrhage can significantly impair vision, particularly those of larger sizes (>1DD) and those located directly below the fovea, and large, foveal sub-macular hemorrhage is associated with poor visual outcomes, particularly if left untreated.[109]

The presence of scar has also been associated with worse visual outcomes in trials, notably the CATT.[87,90] Interestingly, larger hemorrhage (>1DD) was a risk factor for scar development in post-hoc analysis of the CATT, suggesting that part of the poor visual prognosis of these large hemorrhagic lesions may relate to the risk of scarring.[110] Post-hoc analysis of the AREDS2 cohort treated for neovascular AMD also identified fibrosis as being responsible for 40% of the cases of poor vision (<20/200),[111] implying that preventing scar formation remains an important goal in preserving vision.

Treatment Regime and Visual Outcomes

In combination with patient-related factors, decisions made upon and throughout the course of treatment may also influence visual outcomes. Initially, anti-VEGF was approved for fixed dosing every 4 weeks, and this was later extended to 8 weeks as new anti-VEGF molecules with higher binding affinity were discovered.[10,11] In combination with the CATT[14] and IVAN[112] studies, which demonstrated that dosing via a pro re nata (PRN) regimen provided similar visual outcomes, more flexible dosing regimens have been adopted by treating practitioners which has also included the treat and extend (TREX) regime. Under a PRN regimen, patients typically are followed on a monthly basis however at each interval, the decision to treat is guided by disease activity, determined by the presence or absence of exudation. Meanwhile, the TREX regime is considered a proactive approach whereby patients who achieve an exudative-free status on monthly dosing, have their review and treatment interval extended, typically in either 1- or 2-week increments. Upon the presence of exudation, treatment intervals are then reduced, with the goal of maintaining an exudative-free status under the longest possible dosing interval. By design, TREX offers patients with better anatomical outcomes (as there is less recurrence of exudation) and a higher level of individualization, whilst reducing the burden associated with frequent clinical visits. Both the TREX-AMD[113] and CANTREAT[114] studies demonstrated that the TREX regime provided similar visual outcomes to fixed monthly dosing while requiring less injections.

Between PRN and TREX dosing, a systematic review of 70 studies found TREX to provide larger VA gains compared to PRN over a 12-month period (+10.4 vs +5.4 letters respectively), though they received a higher number of injections (8.1 vs 5.6 injections).[115] In the third year of the TREX-AMD randomized trial, those who spent the first 2 years on TREX and switched to PRN for the final year, had significantly worse visual

outcomes compared to those who remained on a TREX regime for the remainder of the study.[116] In a 4-year study, Spooner et al compared progression rates of macular atrophy among 264 eyes treated with anti-VEGF using either PRN or TREX regimes.[117] They found that VA gains among the TREX group were higher compared to the PRN group after 1 year of treatment (+2.7 vs +0.3 letters respectively), however these gains were lost after 4 years (+0.9 vs −0.5 letters, respectively). More long-term prospective data is needed between these two regimes. As data from real-world studies suggest that patients receive fewer injections than those studied in clinical trials, the benefit seen from a TREX regime likely comes from its proactive nature, as a higher number of injections are also associated with better visual outcomes.[28,37,50,118]

Table 3 Summary of Predictive Factors, Their Effects on Visual Outcomes Following Anti-VEGF Treatment and the Level of Supporting Evidence Within the Literature

Baseline Factors	Level of Evidence (Strong, Insufficient or Mixed)	Relationship with VA After Anti-VEGF Treatment
Functional		
Visual acuity	Strong	• Patients presenting with lower VA gain more VA during treatment but are more likely to respond poorly • Those with good initial VA are more likely to maintain good final VA in both the short and long term
Demographic		
Gender	Insufficient	-
Age	Strong	• Older age is associated with worse visual outcomes
Ethnicity	Insufficient	-
Systemic disease	Insufficient	-
Social habits	Mixed	• Current and previous smoking status may be associated with worse visual outcomes
Genetics	Mixed	• The presence of certain AMD risk alleles (CFH & ARMS2) and VEGF polymorphisms may influence visual response
Anatomic		
CNV lesion type	Mixed	• Classic & pre-dominantly classic lesions may be associated with worse visual outcomes due to worse presenting VA.
CNV lesion size	Strong	• A larger lesion size is associated with lower VA gains
Retinal thickness	Mixed	• Markedly thinner or thicker retinas associated with worse VA gain • Fluctuations in thickness are associated with less VA gain and higher risk of atrophy
Retinal exudation	Mixed	• IRF (particularly sub-foveal) associated with worse visual outcomes • SRF at baseline associated with better VA gains, residual SRF associated with poorer outcomes
Pigment epithelial detachments	Mixed	• Presence of PED at baseline associated with worse visual outcomes • Response of PED not associated with VA gain
Atrophy	Mixed	• Presence of macular atrophy associated with worse long-term VA gain
Hemorrhage	Mixed	• Sub-retinal hemorrhage may lead to worse visual outcomes through scar formation

Abbreviations: AMD, age-related macular degeneration; VA, visual acuity; VEGF, vascular endothelial growth factor; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment.

Multivariate Predictive Modelling

Using a combination of OCT biomarkers and VA over the first 3 months of treatment from HARBOR, Schmidt-Erfurth et al[119] used machine learning algorithms to predict 1 year VA outcomes with an accuracy of 71% and an error margin of 8.6 letters. A similar attempt using both VA and OCT data from electronic medical records by Rohm et al,[120] provided comparable levels of accuracy, with errors of 5.5 and 8 letters for predicting 3 and 12 month VA respectively. The incorporation of more predictive variables such as genetic data as well as the examination of larger datasets may provide more precise models in the future. However, because preserving vision is the primary goal of anti-VEGF therapy, rather than quantifying vision, it may be more valuable to develop models which identify non-responders, as this could trigger the earlier consideration of alternative treatment routes such as the switching of anti-VEGF drugs or additional therapy.

Conclusion

Several factors have been found to influence a patient's visual outcome during nAMD treatment (Table 3). However, they play a limited role in the current scope of practice as they do not have the precision in determining whether an individual will respond favorably or not to treatment, nor is there sufficient evidence to guide treatment choices based on individual factors, as the effects of these factors are not associated with certain treatment agents or regimens.

Nevertheless, there are several clinical aspects that can be drawn from these findings. Considering that AMD is a disease of senescence, the strong associations seen for VA, age and lesion size suggests that early detection and timely management is required to achieve optimal visual outcomes. Alongside treatment, exacerbating factors; notably smoking; should also be reduced or ceased if possible, given their possible association with worse visual outcomes, and with AMD progression in general.

Currently, individualized treatment is achieved by using flexible dosing strategies such as PRN or TREX. While these strategies do not necessarily offer superior visual outcomes, they may indirectly improve patient's quality of life and reduce their disease burden through economic relief. These OCT-guided approaches may be further optimized from knowledge of anatomical predictors, as it is suggested that the presence of IRF should be more aggressively controlled in comparison to SRF. While this provides room for further flexibility and individualization during treatment, it is essential that patients remain closely monitored for anatomical changes which may subsequently affect their visual trajectory. Proactive approaches such as TREX appear to be an effective middle-ground.

In the current treatment landscape, currently available agents have been compared based on non-inferiority of visual outcomes. With emerging anti-VEGF agents such as brolucizumab offering longer treatment intervals and greater anatomic outcomes,[121] the consideration of additional markers of efficacy may also be required during treatment decision making. The release of newer therapeutics in combination with further knowledge into predictive factors one day may allow the personalization of more effective treatments for individuals with specific baseline characteristics, disease subtypes or genetic susceptibilities.

Disclosure

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