Baseline Predictors of Visual Acuity Outcome in Patients with Wet Age-Related Macular Degeneration

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1. Introduction

Over the past two decades, eight anti-VEGF drugs have been approved by US Food and Drug Administration (US FDA). Among these, three are commonly used for the treatment of wet age-related macular degeneration (wAMD), which is the leading cause of blindness in people aged over 60 years. Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) was the first VEGF inhibitor approved by the USFDA for treating wAMD in December 2004. It is a selective anti-VEGF RNA aptamer to VEGF-165 but it is no longer widely used due to inferior effectiveness compared to other anti-VEGF agents. In February 2004, VEGF inhibitor bevacizumab (Avastin, Genentech, San Francisco) was approved for the first-line treatment of metastatic colorectal cancer and it also became a commonly used off-label drug for wAMD [1]. Another agent, ranibizumab (Lucentis, Genentech/Novartis) received FDA approval in 2006 for the treatment of wAMD [2]. Another anti-VEGF agent, aflibercept (Eylea, Regeneron/Bayer), was approved by the US FDA in November 2011. It is a fusion protein known as VEGF trap which binds to VEGF-A, VEGF-B isoforms, and placental growth factor (PlGF). The most recent anti-VEGF drug is conbercept (Chengdu Kanghong pharmaceuticals, Chengdu, China), which is another VEGF trap similar to aflibercept. It was approved for the treatment of wAMD by China FDA in December 2013.

Although anti-VEGF therapy has been a breakthrough in the treatment of wAMD, unfortunately, up to a quarter of anti-VEGF-treated wAMD patients might not benefit from intravitreal injections and choroidal neovascularization (CNV) activity does not respond to the treatment. Understanding the predictive factors associated with visual acuity outcome and treatment response to anti-VEGF therapy may help retina specialists to manage patients’ expectations and guide treatment decisions from the beginning of treatment on the basis of “personalized medicine.”
help retina specialists to manage patients’ expectations and guide treatment decisions at treatment initiation. In this review, we discuss various definitions of responder, poor responder, delayed responder, and nonresponder. Preclinical data illustrating the mechanisms of adaptive evasion to anti-VEGF therapy will also be summarized. Finally, we will emphasize the possible predictors to VA improvement and how to achieve the best VA outcome after anti-VEGF therapy for wAMD in clinical practice.

2. Responder, Poor Responder, Delayed Responder, and Nonresponder

A nonresponder is originally defined as a person or animal who does not show any immune response following vaccination against a specific virus. Self-reported tumor resistance to anti-VEGF treatment or so-called nonresponders appears more frequently. An ocular nonresponder to anti-VEGF treatment refers to those patients who developed reduced distance or reading VA compared to baseline during follow-up. These patients can be called “initial nonresponder,” “recalcitrant wAMD,” or “tachyphylaxis.” Lux et al. reported that 45% of the patients with wAMD are nonresponders who underwent intravitreal injections of 1.25 mg bevacizumab and were followed up for 6 months. The nonresponders were defined as follows in this study: (1) reduction in both visual acuity and reading ability at the last follow-up; (2) reduction in either visual acuity or reading ability at the last follow-up; (3) no change in either visual acuity or reading ability at the last follow-up [1]. It has been shown that 14.3% of polypoidal choroidal vasculopathy (PCV) and 14.3% of eyes with wAMD required additional photodynamic therapy (PDT) treatment due to lack of response to intravitreal ranibizumab treatment [2]. The VISION study reported that 40% of eyes with wAMD treated with pegaptanib lost at least 15 letters from the baseline [3]. In the MARINA study, only 34.5% in the 0.3 mg ranibizumab and 42.1% in the 0.5 mg ranibizumab group had better than 20/60 visual acuity [4]. In the ANCHOR study, nonresponder accounted for 10.1% in 0.5 mg ranibizumab-treated eyes which lost at least 15 letters at month of 24 [5]. Nagai et al. [6] defined patients who had no improvement of best corrected visual acuity (BCVA) and lack of reduction of OCT central retinal thickness (CRT) at the end of the initial treatment as initial nonresponders. According to the definition, baseline VA and macular morphology are the two important parameters to assess the treatment response following anti-VEGF therapies. Amoakou et al. proposed the followings as good response to anti-VEGF therapy among wAMD patients: resolution of intraretinal fluid (IRF), subretinal fluid (SRF), and retinal thickening, and/or improvement of at least 5 ETDRS letters. If there was <25% reduction in OCT CRT from the baseline value, with persistent or new IRF, SRF, or minimal or no change in VA (VA change of 0 to 4 letters) after VEGF therapy, it is defined as poor response. Nonresponder could be defined as having increase in fluid (IRF, SRF, and CRT), or increase in hemorrhage compared with the baseline and/or loss of >5 letters compared with the baseline BCVA [7].

3. Polypoidal Choroidal Vasculopathy (PCV) Is More Common among Nonresponders to Anti-VEGF Therapy

Polypoidal choroidal vasculopathy (PCV), characterized by the choroidal vascular abnormalities, was first described by Yannuzzi et al. in 1982. The prevalence varies among different ethnic groups and Asian carries the highest prevalence with up to 53% [8], as compared with the prevalence of around 10% in Caucasian populations [9]. wAMD and PCV share some common clinical features and genetic risk factors. However, the pathological process, natural history, response to anti-VEGF therapy, and treatment outcomes might be quite different.

It has been reported that nearly 50% of nonresponders are misdiagnosed for typical wAMD and PCV accounted for the majority of these cases. As shown by several retrospective observational case series, PCV was the main reason (80–90%) of resistance to anti-VEGF treatment in patients with wAMD [10–12].

The mechanism of the different response to anti-VEGF drugs in eyes with PCV and wAMD is still not fully understood. Pathological studies have revealed that fibrosis and proliferation of retinal pigment epithelium (RPE) cells are more prominent features in wAMD than in PCV and the pathogenesis of polypoidal lesions or the branching vascular network may not purely depend on increased levels of VEGF [13–15]. It has been found that the aqueous humors level of VEGF is significantly lower in eyes with PCV than those of wAMD (P = 0.045); furthermore, levels of PDGF significantly increased in eyes with PCV, wAMD, and pathological myopia, suggesting that the role of VEGF in the pathogenesis of wAMD is greater than in the pathogenesis of PCV [13]. The differential expression level between in patients with PCV or wAMD can at least partially explain why PCV is the majority nonresponder among wAMD patients.

However, a number of studies recently suggested that the response to anti-VEGF therapy in PCV patients may differ according to anti-VEGF drugs. In a retrospective, interventional case series, the effectiveness of intravitreal injection of aflibercept and ranibizumab for patients with PCV was compared. After a 12-month follow-up, there was no significant difference in BCVA between the two groups; however, aflibercept more often led to polyp regression than ranibizumab [16]. Kawashima et al. also found that patients with wAMD or PCV patients refractory to ranibizumab, switching to aflibercept might be more effective regardless of patients’ genotype [17]. Further study with large sample size is warranted to compare the efficiency of different drugs in PCV patients.

4. Mechanisms of Nonresponse to Anti-VEGF Therapy

The mechanism of nonresponse to anti-VEGF therapy is still poorly understood despite being previously studied intensively in cancer research. After the approval of bevacizumab by the USFDA for various cancers treatment including
glioblastoma (GBM), it has been demonstrated that bevacizumab improved the radiographic response, progression-free survival, and quality of life of patients with GBM. However, there are still a proportion of patients who developed resistance and failed to respond to anti-VEGF therapy. Mechanisms postulated to be associated with lack of response to anti-VEGF therapy include (1) activation of the by-pass angiogenesis pathway through upregulation of other proangiogenic factors such as basic fibroblast growth factor (bFGF), stromal cell-derived factor-1 alpha (SDF-1alpha), and platelet-derived growth factor-C (PDGF-C); (2) recruitment of bone marrow-derived stem cells (BMDSC) concomitant with increased level of proangiogenic cytokines and chemokines in the endothelial progenitor (EPC); (3) pericytes progenitors cells (PPC) invading normal tissue areas; and (4) autocrine effects of VEGF signaling promoting tumor invasiveness [14].

Other proposed mechanisms for resistance to anti-VEGF therapy of a tumor cell may be due to the activation of c-Met gene. VEGF receptor (VEGFR) is complexed with c-Met effectors. Hypoxia-induced increase expression of HGF or c-met and prompt ligand independent activation of c-Met. Activation of c-Met gene subsequently induces tumor cell inactivation and transformation [18]. The expression of proangiogenic factors such as angiogenin, IL-lalpha, IL-lbeta, TNF-alpha and TGF-alpha, matrix metalloproteinase-(MMP-)2, MMP-9, and MMP-12 secreted protein acidic and rich in cysteine (SPARC); and tissue inhibitor of metalloproteinase (TIMP) 1 was elevated at mRNA and protein level after anti-VEGF therapy in U87 and NSC23 cell lines and it was found that bFGF was correlated with reactive of tumor angiogenesis [19].

A number of studies have also elucidated the mechanisms of nonresponsiveness following anti-VEGF therapy in ocular diseases. Macrophages induced by anti-VEGF therapy may accelerate the tolerance of anti-VEGF therapy. This may explain the fact that the increased intravitreal dosage of anti-VEGF agents may not contribute and increase the treatment response. Moreover, capillary stabilization in adults is a VEGF independent process. The vascular wall of capillary is surrounded by a single layer of pericytes which stabilizes the vessels during its development and this process is VEGF independent [20]. Finally, the process of angiogenesis is complex and involves multiple molecular and cellular transduction pathways. It has been suggested that VEGF-A is just one of the main pathogenic factors involved in wAMD. PIGF and platelet-derived growth factor (PDGF) have also been shown to be involved in the development of CNV. Animal model has suggested that PIGF, a homologous factor to VEGF, is not essential for physiological angiogenesis but is an important regulator in the pathological angiogenic conditions [21]. Many studies have demonstrated that pericytes share a common basement membrane with endothelial cells and can produce survival factors which shield endothelial cells from anti-VEGF therapy [22–24]. Anti-PDGF has been shown to inhibit angiogenesis in both human and animal studies [25]. Phase Ib trial also demonstrated favorable safety and efficacy profiles of PDGF (pegpleranib) and anti-VEGF drug combination therapy for wAMD across multiple clinically relevant end points [26]. However, the recently released outcomes of two phase III clinical trials using either pegpleranib (Fovista) or ranibizumab both showed no additional benefit in adding anti-PDGF agents when compared with anti-VEGF monotherapy. Further research in the role of anti-PDGF in wAMD is warranted.

Therefore, anti-VEGF therapy alone may play only a partial role in the inhibition of CNV and anti-VEGF agents used in combination with drugs affecting other angiogenesis mechanisms may yield better results. For instance, clinical and laboratory studies suggested that dual inhibition of VEGF and PDGF may be more effective than targeting VEGF alone [25]. Further research is warranted to study the possible role of the elevated level of some particular proteins in the vitreous such as cytokines, chemokines, and other molecular regulators to explain the mechanisms of the resistance to anti-VEGF therapy.

5. Baseline Predictors of Visual Acuity
Outcome in wAMD

5.1. Patients Characteristics. The baseline visual acuity (VA) is one of the most important predictor for final VA outcomes as it will provide the floor or ceiling effect. Patients with worse VA might be correlated with better VA improvement after treatment and patients with better VA are less likely to gain as much due to ceiling effects. In a subgroup analysis of MARINA and ANCHOR study, if the baseline VA in one group is higher than another group by 5 letters, the mean change of VA from baseline to 24 months will be lower by 3.2 letters in the better initial VA group [27]. Vitreoretinal adhesions have also been found to be significantly correlated with poor clinical outcome. Baseline CNV lesion size has been found in several studies to be associated with VA outcomes and large CNV area generally corresponds to poorer visual acuity outcome [27–30]. Several studies have shown that younger age is correlated with better clinical outcomes. In the subgroup analysis of MARINA study, if the average age of one group is younger than another group by 13.7 years at baseline, the change in VA of the younger group will be 5 letters better than the older group [27]. Similarly, subgroup analysis of ANCHOR also showed that younger patients gained more compared with the older group [30]. CATT study also found that patients less than 70 years old gained 10.8 letters, while patients 70 years or older only gained 5.6 letters after treatment [28]. The interval between onset of symptoms and commencement of treatment is another important baseline predictor for final visual outcome and shorter interval from presentation to treatment is correlated with better VA outcomes. It has been shown that patients with a delay in treatment of 21 weeks or more compared to a delay of 7 weeks or less had an odds ratio of 2.62 for worsening vision after treatment, suggesting that longer delay of treatment of commencement was a significant predictor of poorer treatment outcome [29].

5.2. Parameters of Optical Coherence Tomography (Table 1). Optical coherence tomography (OCT) allows noninvasive high resolution imaging of the retina in vivo [31, 32].
Integrity of ellipsoid zone (IS/OS) is highly correlated with VA clinical outcome. Absence or disruption of this layer has been demonstrated to be abnormality of photoreceptor or choroidal diseases [33–38]. It has been found that ellipsoid zone is disrupted in 55%–65% of patients with advanced AMD. In a hospital-based study, eyes with wAMD received intravitreal anti-VEGF treatment. The final visit VA is closely correlated with the integrity of VA. The prognosis VA of patients who have a complete ellipsoid zone is better than those which have partially complete or the invisible ellipsoid zone. Interruption of IS/OS layer is correlated with poor visual prognosis and the length of ellipsoid zone disruption is correlated with different VA outcome [34]. Integrity of external limiting membrane (ELM) is also directly correlated with the VA [35]. Interrupted ellipsoid zone is a sign of the destruction of outer segment of photoreceptor; however, interruption of ELM is a sign of serious damage of inner segment or cell bodies of photoreceptor. In a one-year follow-up of aflibercept treatment on wAMD, the status of ELM is good predictor for visual outcome of wAMD and VA [36, 37]. It has been shown that the integrities of ellipsoid zone and ELM are both correlated with better final VA. Eyes with completely intact ellipsoid layer but disrupted ELM generally have poorer VA (worse than 20/200), indicating that ELM might be a more reliable predictor of VA than ellipsoid zone [38].

It remains controversial whether there is any correlation between foveal retinal thickness (FRT) and VA outcome. It is well accepted that FRT is an early sign and sensitive parameter for detecting reduced baseline VA; however, it is not correlated with the VA outcome [39]. In a hospital-based study with a total of 1105 subjects, in all treatment groups, age, larger CNV area, and greater foveal thickness are negatively correlated with VA outcome [29]. However, another study has shown that central retinal thickness (CRT) is not correlated with VA outcome but is an early sensitive predictor of decreased VA [39]. Patients with intraretinal fluid (IRF) and RPE high reflectivity have been shown to have poor VA outcome [39]. In a 12-month follow-up study, it has been demonstrated that, in eyes that were treated with 3 loading doses of ranibizumab or bevacizumab followed by as needed injections, the mean BCVA was significantly better in eyes with no IRF compared with eyes which had persistent IRF (P < 0.05), while the visual improvement in BCVA was similar between eyes with or without SRF eye [40]. It has been shown that IRF may increase the risk of the formation of geographic atrophy. The 2-year outcome from the CATT study has shown that eyes with IRF under fovea had twice the chance of developing GA and increased subretinal fluid and sub-RPE tissue thickness were associated with a decreased risk for development GA [41]. Results from the subgroup analysis of HARBOR study also showed that, at the 3-, 12-, and 24-month follow-up, SRF is the protective factor for the formation of geographic atrophy compared with the eyes without SRF (2% versus 10%, 5% versus 24%; 8% versus 23%v, respectively) in patients with wAMD [42].

Baseline choroidal thickness might be another important OCT for VA prognosis as it is well accepted that abnormalities of choroidal vasculature are involved in the pathogenesis of wAMD [43]. Age, axial length, refractive error, blood pressure, intraocular pressure, and diurnal variation are influential factors with the thickness of choroid [44]. As there is a relative lack of data from the normal subjects in cohort population study, normal choroid thickness (CT) also varies depending on the method used, and the number of subjects enrolled. In a small case serial study, CT is measured by enhanced depth imaging (EDI) OCT from the posterior border of the retinal pigment epithelium to the choroid/sclera junction at 500 μm to 2500 μm temporal and nasal to the fovea and central 1-mm area of the choroid. The mean central macular thickness was 216.4 ± 30.03 μm and choroid was found to be the thinnest nasally and thickest subfoveally. On multivariate regression, age was the most significant factor affecting subfoveal CT (P < 0.001). Regression analysis showed an approximate decrease in CT of 1.18 μm every year [45]. Manjunath reported that the CT is thinnest nasally, thickest in the subfoveal region, and thicker temporally, with the mean subfoveal CT of 272 μm (SD, ±81 μm) [46]. Increased choroidal thickness has been shown to be closely associated with wAMD [47, 48]. Spectral domain (SD) OCT and swept source OCT provide more accurate information of choroidal thickness by using EDI mode of the imaging software [49]. It has been shown that significant reduction of choroidal thickness is correlated with improved VA after intravitreal treatment of ranibizumab in wAMD patients [50]. Baseline CT is also regarded as a predictive factor of VA.

**Table 1: Prognostic impact of OCT imaging in patients with wAMD.**

| Anatomical structure | Significant findings | Relevant to the clinical outcome |
|----------------------|----------------------|----------------------------------|
| Ellipsoid zone (EZ)  | Absence or disruption| Highly correlated to visual outcome |
| External limiting membrane (ELM) | Interruption | A sign of damage of inner segment of cell bodies of photoreceptors |
| Foveal retinal thickness (FRT) | Thicker than normal | Controversial |
| Features of retinal and RPE layers | Presence of intraretinal fluid | Poorer VA outcome |
| Baseline choroidal thickness (CT) | Thicker subfoveal choroidal thickness | Increase the risk of geographic atrophy |
| Retinal pigment epithelium (RPE) | Double layer sign | Poorer VA outcome |
|                        |                      | A predictor of PCV, higher risk of nonresponse to anti-VEGF therapy |

wAMD: wet age-related macular degeneration.
outcome in patients with wAMD. In a retrospective, consecutive case series study, greater baseline subfoveal choroidal thickness was found to be associated with a better anatomic and functional clinical outcome in eyes with wAMD after intravitreal aflibercept treatment ($r = 0.98$, $P < 0.0001$) [51]. Subfoveal choroidal thickness is also a predictor of macular GA development [52].

Another OCT feature to assess in wAMD eyes is the double layer sign, which is one of the OCT features of PCV indicating abnormal choroidal BVN associated with PED. The dual highly reflective layers can be identified by OCT, one at the level of the RPE and another beneath the RPE. ICGA examination is recommended to rule out PCV in these cases and these cases might potentially be less responsive to anti-VEGF therapy [53].

5.3. Fluorescein Angiography (FA) and Indocyanine Green (ICGA) Findings. FA is useful to document the size of CNV and it has been shown that smaller size of CNV is correlated with good visual prognosis. The MARINA trial showed that if the CNV size in group B is bigger than group A by 3.6 disc area (DA), at the end of study, the VA in group B is lower than group A by 5 letters. ANCHOR study which followed patients for 12 months showed that the lesions increased 1 DA; VA is lower by about 3.54 letters. Furthermore, it was also shown that larger size of CNV is correlated with higher proportion of eyes with complete disruption of the Ellipsoid Zone [30]. FA and ICGA can also evaluate the subtypes of wAMD and these subtypes include classic CBV, predominately classic CNV, occult CNV, PCV, and retinal angiomatosus proliferation (RAP) [54]. Multiple studies have shown that CNV subtypes are correlated with the VA outcomes. In a hospital-based study, 106 patients who received intravitreal anti-VEGF treatment, type I neovascularization at baseline, were more likely to maintain good vision over 4 years [31]. Kang and Roh reported that CNV size not CNV type is correlated with patient's VA outcome [55]. It has also been found that eyes with occult CNV and RAP significantly increase in VA after 3 injections compared to eyes with occult CNV without RAP ($P < 0.01$). No other differences were observed between CNV lesion types regarding VA or change in VA [56].

5.4. Vitreomacular Interface Abnormalities. Vitreomacular interface abnormality (VMIA) in patients with wAMD includes vitreomacular adhesion (VMA), vitreomacular traction (VMT), and epiretinal membrane (ERM). These have been found to correlate with nonresponder to anti-VEGF therapy. It has been found that VMA is more common in eyes with wAMD as compared to control eyes with nonvascular AMD [57–59]. 12.8% of the 1185 patients in the CATT study were found to have VMT or VMA. Progression to GA occurred at a lower rate in eyes with VMT and VMA at baseline (11.7%) compared to eyes without VMT or VMA. On the other hand, a greater number of anti-VEGF injections was required in eyes with VMT or VMA over 2 years, suggesting that the presence of VMA and VMT at baseline is a predictor for nonresponse or tachyphylaxis to anti-VEGF therapy. The localization of VMA or VMT over CNV may hinder the penetration of anti-VEGF agents into the macula. This localization of VMA over CNV also suggests that inflammatory cytokines may participate in the pathogenesis of both CNV and VMA/VMT [53].

5.5. Outer Retinal Tabulation (ORT). Outer retinal tabulation (ORT) is a tubular structure found in the outer retina which can be detected by OCT. In CATT study, the prevalence of ORT was 10.1% at 56 weeks and 17.4% at 104 weeks. The presence of ORT represents degeneration of photoreceptor cell and dysfunction of retinal epithelium cells and mitochondria. It also represents the rebuilding of inner segment of photoreceptors [60]. ORT detected by OCT is correlated with the histological distinguishable structure changes. Schaal et al. found that the location, the composition, and shape of ORT are closely correlated with histological changes (correspondence to four phases of cone degeneration), suggesting that presence of ORT is an indicator of cone degeneration and poor VA outcome [61]. It was shown that intravitreal injection of ranibizumab stabilized ORT and inhibited occurrence of ORT [62] which was a predictor of VA in eyes with center involved diabetic macular edema [63] and wAMD [64]. ORT is also a predictor of the enlargement of geographic atrophy in AMD [65].

5.6. Fibrovascular and Serous Pigment Epithelium Detachment (PED). Fibrous tissue beneath the RPE may block the diffusion of oxygen and other nutrients from the choroidal layer to the retina and also affects the drug penetration from the vitreous to retina and choroid [66, 67]. Suzuki et al. found that fibrovascular PED (OR 33.5, 95% CI 2.95 to 381) is significantly associated with nonresponse to anti-VEGF therapy as judged by both BCVA and fundus findings [66].

5.7. Fundus Autofluorescence (FAF). Detection of fundus autofluorescence is a noninvasive tool which has the potential to predict progression of AMD. Lipofuscin is the fluorophores visualized as by blue light (wavelength 488nm) autofluorescence. Accumulation of lipofuscin has been shown to be correlated with aging and progression of wAMD [68]. Imagine detection of FAF together with OCT and FA are routine investigations performed in clinical trials of wAMD. FAF image provides useful information reflecting RPE functions. Although FAF is more widely used for dry AMD, it is generally accepted that an intact normal foveal FAF is a good predictor for response to anti-VEGF therapy [69]. Better VA improvement is correlated with less abnormality in FAF. Increased FAF indicates excessive accumulation of lipofuscin in RPE and poorer visual prognosis. Reduced FAF may suggest apoptosis of RPE and dysfunction [70].

6. Predictive or Pharmacodynamics and Biomarkers

Drug-related biomarkers (drug metabolizing enzymes, transporters and targets, etc.) and genetic polymorphisms have been evaluated as factors influencing drug effectiveness or individual differences in drug response. Successful completion of Human Genome Project is a strong impetus to the expansion of clinical medicine from the macro to micro areas...
and from cell to molecular level. In recent years, many studies have shown that biomarkers provide a good prognosis for the patient’s individualized treatment, indicating that research has been taken into the molecular diagnosis of wet AMD and individualized treatment era.

7. Gene Variant

Genetic variants are potentially promising predictors for prognosis after anti-VEGF therapy for AMD. It has been found that a higher frequency of the risk (T) allele (Allelic $P = 0.019$) and TT genotype ($P = 0.002$ under a recessive model) for the VEGFA-rs943080 polymorphism are correlated with nonresponse to anti-VEGF therapy. VEGFA expression was 1.8-fold higher in cells with the VEGFA rs943080 TT genotype than in cells with the VEGFA rs943080 CC genotype ($P = 0.012$) [71]. Orlin et al. reported that single-nucleotide polymorphism rs1061170, rs10490924, rs3750848, rs3793917, rs12200638, and rs9322725 and for the indel del443ins54 spanning the CFH, ARMS2, and HTRA1 genes are correlated with negative response after anti-VEGF therapy [72]. It was also found that individuals with genotype CC of p.Y402H in CFH had less chance of positive treatment outcome compared with those with the CT and TT genotypes ($P = 0.005$ and $P = 0.006$). In this study, the genotype combination of AG at CFH with CT at FZD4 (SNP rs10898563) was found to have an increased chance of positive treatment outcome ($P = 0.004$) [73]. Another study suggested that polymorphism rs1061170 in the CFH gene is a predictor of treatment response to anti-VEGF drugs [72].

8. Management Strategies for Nonresponders to Anti-VEGF Therapy Combination Therapy

Multiple studies have shown that combination therapy, administered in dual or triple combinations (corticosteroids, verteporfin photodynamic therapy, and anti-VEGF agents), might have more advantages compared with anti-VEGF monotherapy, especially in terms of reducing the need for retreatment. This is especially important for the PCV subtype of wAMD as the influence of VEGF appears to be lower in PCV. Another rationale of performing combination therapy is the potential increased expression of VEGF in PCV patients following PDT and anti-VEGF therapy which can counteract this post-PDT increase in VEGF production [14]. FOCUS study is the first clinical trial to evaluate the efficiency of combination anti-VEGF therapy with PDT in patients with wAMD. The result showed that, at month 24, 88% ranibizumab combined with PDT therapy patients lost <15 ETDRS letters from baseline VA compared with the PDT treatment alone and had low rate of adverse event [74]. Similarity, the MONT BLANC study reported that intraretinal cysts or SRF decreased significantly more in the combination group than the monotherapy anti-VEGF alone. Intraretinal cysts were the only relevant prognostic parameter for functional outcome [75]. EVEREST II study showed that VA improved by 8.3 letters in the combination therapy group compared with the 5.1 letters of the ranibizumab monotherapy group. The complete regression rate of polyps is also significantly higher than in the combination group compared with the ranibizumab monotherapy group, suggesting that initially combined therapy can be considered as the first-line treatment strategy for PCV [76]. In the DENALI study, it was shown that ranibizumab monotherapy or combination with PDT improved VA at 12 month, furthermore noninferiority (7-letter margin) of combination regimens to ranibizumab monotherapy was not shown [77]. In the PLANET study for PCV, it was demonstrated that aflibercept monotherapy with sham rescue PDT was noninferior to aflibercept combined with active rescue PDT in terms of visual acuity gain over 2 years. At week 52, both treatment arms gained over 10 letters from baseline, and the visual acuity gain was maintained until week 96. CST reduction from baseline was similar between the two treatment arms and polyps showed no activity in over 80% of patients. Nonetheless, PLANET study required fixed dosing of aflibercept with initial 3 loading doses at monthly interval followed by 2 monthly injections during the first year and it was unclear whether as needed treatment with aflibercept could achieve similar results.

9. Switch to Different Anti-VEGF Agents

Switching of anti-VEGF drugs can be considered in nonresponders following treatment of wAMD [69]. Ehlken et al. reported that nonresponders may benefit from switching to other drugs either to bevacizumab or ranibizumab. In this study, VA at the time of the switching, anti-VEGF therapy was the only prognostic factor for the progress of VA and positively correlated with the beneficial improvement of VA by linear regression analysis [69]. VA at the time of the switch was positively correlated with a beneficial development of VA after changing the drug. In addition, significant anatomical and visual benefits could be in nonresponders when switching from bevacizumab to ranibizumab [70]. Lucio-Eterovic et al. suggested that switching nonresponders to aflibercept may be a good option after failed ranibizumab or bevacizumab therapy [18]. Further research in a large population is warranted.

10. Summary

In conclusion, age, baseline vision, OCT features, and genetic polymorphisms at baseline might be potential prognostic predictors for VA in patients with wAMD. Genetic factors might be the causes for the variations in drug reactions among different individuals and races. With improvements of genomic technology platforms, better correlations of genotypic and phenotypic findings can be identified and this will allow better use of pharmacogenomics in individualizing therapy.

Innovation in the biochemical field has led to substantial clinical progress. The development and availability of new drugs and biological products will allow novel treatment options for patients, especially for those nonresponders to anti-VEGF therapy. Currently, there are several new drugs
which underwent the preclinical, Phase I–III investigations: abicipar pegol, a recombinant protein of the designed Ankyrin repeat protein (DARPin, Allergan) family, is an antagonist of VEGF-A that inhibits all relevant subtypes of VEGF-A with high potency. In the phase 2b PEACH study for wAMD, it was reported that abicipar pegol provided at least equal or higher vision gains with the potential for fewer injections in compared to the standard of care treatment ranibizumab. Brolucizumab (ESBA1008, ALCON) was shown by OSPREY phase II study to have the similar effects with aflibercept. Inhibition of angiopoietin 2 involved in the transmembrane tyrosine kinase protein Tie2 pathway has been shown to reduce vascular leakage and inhibit angiogenesis in mouse model of wet AMD. A phase 1 trial which evaluated the drug RG7716 (Roche), a bispecific monoclonal antibody to VEGF and angiopoietin 2, has demonstrated good safety with positivity biologic signals in terms of both VA and anatomical improvements in patients with wet AMD [78]. Furthermore, more than 20 new drugs are currently under clinical investigations including X82 (Tyrogenex), GB 102 (Graybug), OHR-120 (Santen), and THR-317 (Thrombogenics) for the treatment of wAMD. Further basic medical research and the rapid development in the field of biotechnology will provide critical insight into the clinical applicability of new regimens for the treatment of wAMD.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| AMD | Age-related macular degeneration |
| bFGF | Basic fibroblast growth factor |
| cFDA | China FDA |
| CNV | Choroidal neovascularization |
| CRT | Central retinal thickness |
| ELM | External limiting membrane |
| ERM | Epiretinal membrane |
| FVPED type | Fibrovascular RPE detachment |
| GBM | Glioblastoma |
| IRF | Intraretinal fluid |
| nAMD | Neovascular AMD |
| OCT | Optical coherence tomography |
| ORT | Outer retinal tabulation |
| PDGF | Platelet-derived growth factor |
| PED | Pigment epithelium detachment |
| PIGF | Placental growth factor |
| RAP | Retinal angiomatus proliferation |
| RPE | Retinal pigment epithelium |
| SD OCT | Spectral domain OCT |
| VEGFR | VEGF receptor |
| VMA | Vitreomacular adhesion |
| VMIA | Vitreomacular interface abnormalities |
| VMT | Vitreomacular traction |
| wAMD | Wet AMD |

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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