8 Management Strategies for Neovascular AMD

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8.1 The Story of Anti-VEGF Treatment: Molecules and Regimens

The current treatment of neovascular age-related macular degeneration (nAMD) is mainly based on the inhibition of the vascular endothelial growth factor (VEGF) in the retinal tissue by intravitreal injection of anti-VEGF agents. This approach allowed for the first time in history, a mean visual improvement from treatment start (baseline) [1–3], whereas preceding treatment options such as laser photocoagulation or photodynamic therapy (PDT) with verteporfin were only able to reduce the degree of visual loss. Although both laser and PDT are still occasionally used, these treatment options are reserved for exceptional cases.

VEGF was identified in the 1990s as a key factor in the development of neovascular membranes [4, 5]. VEGF was not only sufficient to promote a neovascular response [5] but also required; when VEGF was blocked in a nonhuman primate, no vasoproliferation was detected [4]. Subsequent studies have well established the central role of VEGF in neovascular disorders. The first commercially available anti-VEGF molecule was *pegaptanib* (brand name Macugen), licensed in 2000. It showed in a phase 3 clinical study an efficacy for nAMD which was yet limited to a reduction in visual loss compared to sham [6], similar to the efficacy of PDT with verteporfin [7]. Pegaptanib is a molecule that competitively binds to the VEGF isoform 165, which was considered the main pathogenic isoform. However, later studies showed that this approach neglected other VEGF isoforms with significant pathogenic potential that need to be targeted as well. *Ranibizumab* (brand name Lucentis), a specific affinity-mature fragment of a recombinant humanized IgG1 monoclonal antibody that neutralizes all active VEGF-A isoforms of the human VEGF protein, was licensed in 2006. With its arrival, a true efficacy revolution was started: Using monthly intravitreal injections, a mean visual acuity improvement was obtained after 1 and after 2 years of treatment, ranging between a mean gain of 5.4 ETDRS letters and 11.3 letters according to the study [1, 2, 8].

These pivotal trials did set the reference for the best visual outcomes under currently available treatment options. This astounding improvement in the prognosis of nAMD was achieved on the basis of *fixed monthly injections*. The high treatment frequency placed a heavy burden on the management of patients with chronic nAMD, thereby requiring many clinical and therapeutic interventions over the course of a patient's lifespan due to the repetitive treatment scheme.

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Therefore, many attempts were made to reduce the burden, both on the level of the total number of injections (cost factor) as well as on the level of the number of monitoring visits (human and technical resource factor). Quarterly fixed ranibizumab injections resulted in a loss of the initial VA improvement and were shown to be significantly inferior to monthly injections, although a subset of patients did well on this regimen [9–11]. A small study with the first *pro re nata (PRN) dosing* showed the feasibility and efficiency of a re-treatment strategy based on monthly assessments of visual acuity, fundus examination, and most importantly optical coherence tomography (OCT), allowing for a reduction in the mean number of injections [12, 13]. However, the inter-individual range of treatment needs varied widely, between monthly injections and no re-treatment after the loading dose. A later study showed that the mean treatment interval in a PRN regimen is approximately 2 months for ranibizumab [14]. The PRN regimen was the first approach to be widely adopted in clinical practice. It was validated as a valuable treatment option with a non-inferior outcome as compared to a fixed monthly re-treatment [15]. Both ranibizumab and the entire antibody *bevacizumab* were shown to be adequate treatment options [15]. However, some differences were found favoring ranibizumab: Pathological fluid was less frequently present when using ranibizumab, and the functional outcome of ranibizumab in the fixed monthly treatment was significantly better than bevacizumab in a PRN regimen [15]. In addition, bevacizumab is not licensed for intravitreal use but for intravenous use in oncology. In conclusion, bevacizumab is a less expensive second-choice off-label anti-VEGF drug, which has shown close to optimal efficacy for intravitreal use in nAMD.

Aflibercept is a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of the human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin. Aflibercept was first labeled in 2011 for an intravitreal use in nAMD. The pivotal phase 3 clinical trial used in the first year a fixed injection regimen every 2 months for aflibercept (as compared to monthly injections with ranibizumab) and a PRN regimen in the second year. In both study periods, the efficacy of aflibercept was equivalent to that of ranibizumab. Thus, aflibercept was labeled for intravitreal injection in nAMD, and the recommended regimen was a fixed injection every 2 months. Although this is a valid approach, concerns were raised due to a subset of patients with significant monthly recurrences, leading to a zigzag curve of structural OCT outcomes when treating every other month [15]. It is unclear whether these patients would have had a better functional outcome with a monthly instead of the bimonthly aflibercept treatment.

Very recently, the new anti-VEGF agent *brolucizumab*, a very small single-chain antibody fragment allowing a high drug concentration, has shown its efficacy in a phase 3 study. The non-inferiority in comparison to aflibercept was shown for visual acuity and structural results, although the regimen was based on fixed injections every 3 months. Apparently, this new molecule might have a long-lasting activity, possibly related to the higher molecular dose. However, roughly half of the patients showed some disease activity when treated at 3-month intervals, and their regimen was changed to an injection every 2 months. Brolucizumab has recently become available on the market.

While fixed regimens have the major advantage of the ability to plan ahead with little necessity for monitoring visits, they result inevitably in overtreatment of some patients and/or undertreatment of others due to the large variability in treatment needs. In addition, economic concerns, limited resources, and considerations regarding possible side effects of the intravitreal injection procedure (endophthalmitis) lead to an inclination to reduce the number of injections. Individually adjusted variable dosing regimens have the potential to respond adequately to these requirements. Variable dosing regimens aiming for an individualized treatment, use the minimum number of injections needed for the best possible outcome. Independent of the choice of the anti-VEGF agent, variable dosing regimens rely on best practice in terms of *visit intervals and*

re-treatment criteria. Major efficacy losses arise if the follow-up is neglected or unsuitable re-treatment criteria are used. Real-life results of PRN regimens have shown that visit interval longer than a month are unsuitable to achieve the best outcome. This is not surprising, as not only the treatment needs are extremely variable among patients, but longer monitoring intervals in a PRN regimen lead in many patients also to protracted recurrence periods. Thus, re-treatment may come too late in order to prevent progressive retinal damage due to recurrence. In other words, PRN with anti-VEGF antibodies is only a valuable strategy if monthly monitoring visits and prompt re-treatment in case of a recurrence can be guaranteed. The re-treatment criteria are discussed in a separate paragraph below.

The need for strict monthly monitoring visits in a PRN regimen with anti-VEGF drugs has rapidly revealed the capacity limits of healthcare providers. The high incidence of new cases and the required treatment chronicity have led to an overwhelming number of patients to be cared for. Moreover, PRN has the major disadvantage that planning is impossible, which is a logistic challenge to the institution and a psychological burden for the patient. Thus, alternative regimens have been developed, based on the idea that the past experience with a given eye may allow anticipating the future need for injections.

The *treat-and-extend regimen* applies this idea. After a loading dose of one to three monthly injections, the treatment interval is progressively extended by 2 weeks as long as no signs of activity (the criteria are discussed below) are detected. Monitoring is performed immediately before an injection, and its result determines the length of the next interval, without modifying the planned imminent injection. As soon as a monitoring visit reveals any signs of activity, the interval is shortened by 2 weeks. The interval between visits combining monitoring with treatment should usually not exceed approximately 3 months (12–16 weeks). If the macula of a treated eye remains dry at this three-month interval, a choice between the default treatment every 3 months or a change to monitoring visits without injections every 2 months is suggested. The outcomes with this strategy are comparable to those with a PRN regimen and statistically non-inferior to monthly re-treatment [16]. The treat-and-extend regimen needs a significantly lower number of monitoring visits (the mean value is approximately eight per year), and planning is clearly facilitated as nearly each monitoring visit goes along with an injection. Thus, this strategy has been widely adopted as the first-choice regimen for anti-VEGF treatment in nAMD.

The *observe-and-plan regimen* also applies the idea to schedule treatment intervals, however, to a series of injections instead of single injection intervals. Based on the regularity of individual treatment needs [17], the observe-and-plan regimen evaluates after the loading doses the time to the first recurrence signs using monthly monitoring visits ("observe"), thereafter applying this interval slightly shortened by 2 weeks in a series of planned injections with a fixed interval (up to three injections, interval between 1 and 3 months, treatment plan up to 6 months) [18, 19]. The monitoring visits after a series of fixed injections are therefore less frequent (the mean being approximately four per year) than in the treat-and-extend regimen, and the ability to plan ahead is excellent. However, the longest treatment interval without a monitoring visit should not exceed 3 months. This regimen has the potential for excellent patient care with limited ressources.

8.2 Re-Treatment Criteria for Variable Dosing Regimen

Sensitive re-treatment criteria are the cornerstone of any variable dosing regimen with anti-VEGF drugs. Most studies consider primarily OCT criteria, combined with fundus examination and visual acuity loss.

- *Visual acuity*: Visual loss relative to any preceding monitoring visit (typically 5 ETDRS letters or 1 line) is a clinically meaningful but unreliable criterion for re-treatment with anti-VEGF drugs. This re-treatment criterion was used due to its ease of examination. However, pathological changes are usually first detectable by OCT and manifest as a decline in

visual acuity later. In addition, vision loss may be caused by many other conditions than exudative recurrence, and they may be completely unresponsive to anti-VEGF treatment, such as progressive macular atrophy or cataract. Therefore, it cannot be a stand alone criterion. In addition, retreatment should not wait for visual loss to happen, if other signs of activity are present. For best functional results it is important to treat before irreversible damage occurs to the photoreceptors.

- *OCT criteria*: With the arrival of high-precision spectral-domain OCT (SD-OCT) allowing a precise examination of the entire 6 × 6 mm macular cube, OCT has become the cornerstone of re-treatment strategies. Any pathological retinal fluid is easily detected by scanning through all acquired B-scans. However, a single line would be insufficient for decision making, as not only the fovea but also extrafoveal areas are relevant, needing treatment to prevent further neovascuar growth. Intra- or subretinal fluid is commonly considered a solid re-treatment criterion because it is usually a sign of active exudation from the neovascular membrane, requiring anti-VEGF re-treatment. However, fluid under the retinal pigment epithelium is only by some studies considered a re-treatment criterion [15]. This type of fluid is - after an initial improvement - insufficiently responsive to anti-VEGF treatment and appears to be not relevant for re-treatment. Considering this type of fluid a re-treatment criterion does not change the visual prognosis. However, cases of high retinal pigment epithelium detachment generally require anyway a high number of injections as intra- or subretinal fluid is frequently present and poorly responsive.
- *Retinal hemorrhage*: The fundus examination is the most useful investigation technique to identify retinal hemorrhage. New retinal hemorrhage may be a sign of nAMD activity requiring anti-VEGF re-treatment. Most variable dosing regimens consider a new hemorrhage to be a re-treatment criterion. However, hemorrhage might occur independently of VEGF levels and may not necessarily represent nAMD activity. For instance, large neovascular feeder vessels in combination with systemic hypertensive peaks or sustained Valsalva pressure might be the cause. Thus, hemorrhage might occur even under monthly anti-VEGF treatments and a complete VEGF suppression.

In summary, SD-OCT is the most important investigation for variable dosing regimens with anti-VEGF drugs. The general strategy is to apply the minimal number of injections in order to nearly completely suppress VEGF activity. Re-treatment is indicated at the earliest signs of exudative recurrence such as the presence of intra- or subretinal fluids, in particular foveal fluids. However, even extrafoveal fluids represent a threat to visual acuity due to underlying reactivation of neovascular processes. Any such reactivation might ultimately lead to further growth of the neovascular complex. As this could result in further loss of vision, any identification of relevant fluids is considered a criterion for re-treatment in order to prevent a disease progression.

Recent studies revealed a difference in the functional and prognostic relevance of intra- versus subretinal fluids. It has been shown that intraretinal fluids are associated with a worse visual outcome, whereas subretinal fluids appear to be well tolerated [20, 21]. Another recent study revealed that subretinal fluids up to 200 µm can be tolerated even under the fovea without a visual disadvantage, and the authors found non-inferiority versus no fluid tolerance [22]. Thus, the re-treatment criteria in variable dosing regimens with anti-VEGF drugs for nAMD might undergo some changes in the near future, differentiating the roles of subretinal from those of intraretinal fluids.

Some open questions still need to be addressed:

- *Degenerative* fluid accumulation due to a loss of retinal substance might simulate exudative fluids. However, reliable criteria to differentiate between them are missing. The best indicators of degenerative fluids might be so far: non-responsiveness to anti-VEGF drugs, overlying atrophy or fibrosis, no retinal thickness increase, and small intraretinal spaces.
- A subset of eyes presents *refractory fluids despite monthly treatments* with anti-VEGF medication. The causes of such a refractory fluid are variable and often difficult to identify.

Some patients might just have high intraretinal VEGF levels and an early recurrence, requiring ongoing monthly re-treatment with anti-VEGF drugs, while others might have a pathological exudation of an origin other than VEGF, being completely non-responsive to anti-VEGF treatment and, thus, not requiring monthly anti-VEGF injections. A non-responsive fluid might be linked to inflammation, degenerative changes, central serous chorioretinopathy, polypoidal choroidal vasculopathy, or other disorders. Obviously, adjuvant or alternative treatment strategies could be considered according to the cause of the refractory fluid. Steroids will be most useful in cases involving inflammatory components, while PDT with verteporfin would be an interesting treatment adjuvant for polypoidal choroidal vasculopathy (recently termed aneurysmal type 1 neovascularization). A triple therapy combining anti-VEGF medication with both intravitreal steroids and PDT has also been suggested.

- The role of switching from one anti-VEGF molecule to another has been largely discussed in the literature, however, without a convincing conclusion. It seems that refractory cases might sometimes benefit from changing the anti-VEGF agent, and drug tolerance may play a role [23]. However, clear clinical indicators are missing.
- The degree of structural and functional damage to the retina is currently poorly taken into account in the treatment regimen. Progressive fibrosis and atrophy are the main reasons for progressive visual loss despite careful re-treatments with anti-VEGF drugs [24]. Anti-VEGF treatment only addresses the exudative part of the disorder. However, if visual loss becomes severe (<0.1) due to irreversible fibrosis or atrophy, the usefulness of continued intravitreal injections is very limited. At some point, the anti-VEGF treatment does not make sense anymore. In the absence of a clearly defined limit, most clinicians will abandon the treatment when the vision is reduced to counting fingers.
- The topographic correlation between exudation and structural–functional retinal damage is another point that has so far been poorly addressed by variable dosing regimens with anti-VEGF drugs. While there is an agreement that exudative fluid should be treated independently of its location with respect to the fovea, it might well be that a location within a nonfunctional atrophic or fibrotic area is not a good re-treatment criterion: As long as functional regions of the retina are not threatened by exudation or neovascular membrane growth, it might not be needed to insist on VEGF suppression. However, the available evidence is insufficient to give recommendations on this point.

8.3 Screening and Early Discovery

Anti-VEGF treatment has introduced a new era in the treatment of nAMD improving its prognosis. Its efficacy with strong control over exudation and vasoproliferation allows for good visual acuity improvements as compared to the treatment baseline. The relative improvement is particularly good in eyes with poorer baseline vision [25]. However, the resulting vision level is the most relevant outcome for patients. Even if a lower baseline vision gains statistically more with anti-VEGF drugs, the resulting visual acuity remains lower than that of an early treated nAMD. A long-standing untreated nAMD will show more fibrosis and irreversible retinal damage, limiting the potential functional gain of any treatment. Thus, it is well recognized that the *early discovery of a neovascular complication in AMD* is extremely important for the final visual outcome.

A variety of screening approaches are available for the clinician and the patient. Clinical visits with visual acuity and SD-OCT are sensitive, but they cannot be performed frequently enough for efficient screening. The cornerstone of screening is the *home monitoring* of well-educated patients. The oldest method goes back to Prof. *Amsler*, who developed a simple *grid* with a central fixation point, printed on paper, to identify *metamorphopsia* (monocular examination reading correction and reading illumination). The appearance of new metamorphopsia is an early sign of retinal deformation, usually in the context of macular edema. In a patient with known early signs of AMD such as drusen and pigmentary changes, there is a high

probability that new metamorphopsia indicates early exudative changes of nAMD. Such a patient needs to be seen by an ophthalmologist as soon as possible within 2 weeks.

Recently, a specially designed home monitoring device (ForseeHome™) has been tested for its sensitivity and specificity in the screening of neovascular complications in AMD [26]. It uses preferential *hyperacuity perimetry*. The use of this device led to the earlier recognition of neovascular complications and a better visual outcome than regular office visits (in combination with the Amsler grid at the discretion of the investigator). It is the first commercially available device for this use and approved by the US Food and Drug Administration (FDA).

In recent years, many *electronic applications* have emerged, proposing nAMD screening based on both Amsler grid analysis and hyperacuity perimetry. There are many minor and major variations available, and it is impossible to give clear recommendations for one or the other application. However, a minimum of scientific evaluation should be required in order to guarantee the quality of size, contrast, color setting, etc. Approval by the FDA is available for some of the applications.

8.4 Safety of Anti-VEGF Treatment

Anti-VEGF treatment for nAMD is applied using intravitreal injections. Both ocular and systemic safety concerns of the drug and the injection procedure need to be considered.

Safety issues of systemic treatments, including arterial hypertension and thromboembolic events, are not applicable in the same way as the eye globe is a relatively closed system. However, small quantities of anti-VEGF antibodies are absorbed into the systemic circulation, and in some patients, the systemic VEGF levels were critically reduced by 50%. However, the reported rates of systemic adverse events are low in all studies. No study showed a significant difference between anti-VEGF and comparison arms. However, minor nonsignificant differences with slightly more cardiovascular events in the anti-VEGF arms have initiated meta-analysis studies. In a meta-analysis including 21 studies with 9557 patients, anti-VEGF treatment did not significantly increase overall mortality or cardiovascular mortality [27]. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups.

Ocular inflammation and increased intraocular pressure after intravitreal injection were the most frequently reported serious ocular adverse events [28]. Endophthalmitis was reported in fewer than 1% of anti-VEGF-treated participants; no cases were reported in control groups. The transient increase in intraocular pressure after intravitreal injection of 0.05 ml of the anti-VEGF drug might need special consideration in advanced glaucoma patients with low target pressure.

8.5 Combination Treatment and Alternative Treatment Options

Anti-VEGF monotherapy is currently the best available treatment strategy for nAMD. Its strong control over exudation and vasoproliferation results in a high level of disease control. No alternative or adjuvant treatment has been able to improve this excellent outcome further. However, nAMD is a complex, multifactorial disorder. Therefore, it appears attractive to add a second line of action by an adjuvant treatment, potentially complementary to the anti-VEGF action. So far, no combination treatment was able to improve the visual results. Recently, the promising approach of combining anti-VEGF antibodies with pegpleranib E10030 (Fovista), an anti-platelet-derived growth factor antibody, failed to reach superiority to anti-VEGF monotherapy (ClinicalTrials.gov Identifier: NCT01940900), although its pathophysiological basis was highly attractive (acting on pericytes in semi-mature neovessels in order to increase the anti-VEGF sensitivity).

However, several other combination therapies are able to reduce the number of anti-VEGF injections. This appears to be particularly

attractive for the so-called "anti-VEGF-refractory nAMD." However, little is known about possible unwanted effects on visual acuity in these cases. This would be important to avoid unnecessary additional risks of unwanted effects due to adjuvant treatments.

PDT with verteporfin was the standard treatment for subfoveal nAMD before the arrival of anti-VEGF drugs. Although it improves the final outcome compared to sham to some extent, a loss in the mean visual acuity was still a reality and the efficacy, therefore, not satisfactory [29]. However, in cases of a contraindication of the anti-VEGF treatment for whatever reason, PDT might be an alternative to reduce visual loss, but patients need to be informed about its inferiority compared to anti-VEGF therapy.

The *combination of anti-VEGF drugs with PDT* has been investigated in numerous studies. A recent meta-analysis included 16 randomized controlled trials comparing anti-VEGF monotherapy and the combination treatment of anti-VEGF antibodies with PDT (standard or reduced fluence) [30]. This meta-analysis confirmed that they only differed in the number of anti-VEGF injections needed, whereas visual acuity and central retinal thickness changes did not differ [30]. Interestingly, a subgroup analysis of adjuvant full-fluence PDT did reveal a lower central retinal thickness. This could be a warning sign, as full-fluence PDT has the potential to damage the choriocapillaris and the pigment epithelium.

Particular interest has been given to the role of PDT in *polypoidal choroidal vasculopathy (PCV)*, a special subtype of nAMD. Before the arrival of anti-VEGF therapy, PDT showed some promising results in PCV [31], while being relatively poorly efficient in other types of nAMD. Since the arrival of the anti-VEGF treatment, an improved visual benefit was found not only for nAMD in general but also for PCV. However, several studies have shown in PCV an interesting potential of anti-VEGF drugs with adjuvant PDT [32]. Their results are moderately variable; some of them suggesting a superior visual outcome and a higher rate of polyp closure along with a decreased number of anti-VEGF injections in the combination therapy [33], whereas others found a very high rate of disease control in anti-VEGF monotherapy with no added benefit from additional PDT treatment [34]. Thus, both options are currently considered valuable treatment approaches. In a setting with readily available anti-VEGF medication, PCV patients will undergo anti-VEGF monotherapy as a first-line treatment and change to a combination with PDT in case of persisting exudative signs. However, in cases with a priority for reduced numbers of injections and appointments, the first-line combination of anti-VEGF drugs and PDT might be an interesting option. However, this approach requires indocyanine green angiography for diagnosis and treatment guidance.

A broad combination treatment with *anti-VEGF antibodies, PDT, and intraocular steroid injections* (triamcinolone) has also been proposed as the so-called triple therapy [35]. The rationale combines the anti-VEGF and anti-inflammatory effects to act on both the neovascular processes and the PDT-related unwanted effects, increasing the benefits of adjuvant PDT on vascular occlusion. Although this treatment has been reported to be beneficial, there is no controlled clinical trial available. Therefore, no clear recommendation can be made. This treatment option might be of interest in some highly exudative, anti-VEGF-refractory cases.

The combination of anti-VEGF medication with *stereotactic radiotherapy* has been investigated in nAMD eyes with high anti-VEGF demand. The INTREPID trial found a reduced number of anti-VEGF injections over 2 years following a single stereotactic radiotherapy session [36]. However, some radiation-related unwanted effects were also described but considered non-significant for visual outcomes. Currently, a larger clinical trial is underway (ClinicalTrials.gov Identifier: NCT02243878), and first results might be expected for 2024.

Large submacular hemorrhage is a particular challenge in the management of nAMD. Dramatic visual loss occurs if the hemorrhage is central, and photoreceptors rapidly suffer from irreversible damage when in direct contact with a thick layer of blood (subretinal hemorrhage). In such cases, a combination of vitrectomy, subretinal

tissue plasminogen activator, and intravitreal gas might be considered, if the bleeding is very recent. Outcomes vary widely, and systematic trials are lacking [37].

Very recently, the mineralocorticoid receptor pathway has been suggested to be implicated in the pathogenesis of choroidal neovascularization, based on animal models [38]. The clinical application has only been tested in a clinical pilot study [38] but may potentially become an interesting future option.

8.6 Future Challenges

Despite the breakthrough in the nAMD prognosis due to anti-VEGF treatment options, there are many unmet needs in nAMD. The underlying degenerative process frequently leads to macular atrophy and profound visual loss despite "successful" control of the neovascular process. Fibrosis is not inhibited by anti-VEGF treatment, a major problem particularly in type 2 neovascularization (classic neovascular membrane), and responsible for irreversible visual losses. Massive macular hemorrhage may occur in nAMD despite maximal monthly re-treatment with anti-VEGF medication, causing a profound acute loss in visual acuity. The chronicity of the exudative disorder requiring repetitive intravitreal injections is a major problem for patients and healthcare providers. More durable and less expensive solutions would be beneficial. Long-term delivery systems or small interfering RNAs are promising future possibilities. Artificial intelligence might become a useful tool to monitor and manage large numbers of patients. Finally, it could become a reality to recover lost vision with stem cell techniques or artificial retinal implants. Obviously, the best solution would be to find an efficient prophylactic treatment to prevent that AMD compromises the vision.

Key Learning Points

- The clinical management of nAMD requires careful monitoring and sensitive re-treatment criteria for anti-VEGF treatment. SD-OCT plays a key role in follow-up and decision-making.
- A variety of treatment regimens are available to the clinician. The key to functional success is not the choice of the regimen but the careful application of its rules, including monitoring intervals and re-treatment criteria.
- Undertreatment threatens the vision more than overtreatment.
- Most importantly, early discovery is crucial for good final visual results. Screening methods and patient education are most helpful.
- Some cases do not entirely respond to anti-VEGF treatment. Their best management is not well established. Combination treatment with other modalities may be considered.

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