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# Age-related macular degeneration: Beyond anti-angiogenesis

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Recently, anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration have been developed. These agents, originally developed for their anti-angiogenic mechanism of action, probably also work through an anti-permeability effect in preventing or reducing the amount of leakage from submacular neovascular tissue. Other treatment modalities include laser photocoagulation, photodynamic therapy with verteporfin, and submacular surgery. In reality, these latter treatments can be similarly categorized as anti-angiogenic because their sole aim is destroying or removing choroidal neovascularization (CNV). At the cellular level, CNV resembles stereotypical tissue repair that consists of several matricellular components in addition to neovascularization. In the retina, the clinical term CNV is a misnomer since the term may more appropriately be referred to as aberrant submacular repair. Furthermore, CNV raises a therapeutic conundrum: To complete or correct any reparative process in the body, angiogenesis becomes an essential component. Anti-angiogenic therapy, in all its guises, arrests repair and causes the hypoxic environment to persist, thus fueling pro-angiogenesis and further development of CNV as a component of aberrant repair. However, we realize that anti-vascular endothelial growth factor therapy preserves vision in patients with age-related macular degeneration, albeit temporarily and therefore, repeated treatment is needed. More importantly, however, anti-angiogenic therapy demonstrates that we can at the very least tolerate neovascular tissue beneath the macula and preserve vision in contrast to our historical approach of total vascular destruction. In this clinical scenario, it may be possible to look beyond anti-angiogenesis if our goal is facilitating submacular repair without destroying the neurosensory retina. Thus, in this situation of neovascular tolerance, it may be timely to consider treatments that facilitate vascular maturation, rather than its arrest or destruction. This would neutralize hypoxia, thus removing the stimulus that drives neovascularization and in turn the need for repeated lifelong intravitreal therapy. A pro-angiogenic approach would eliminate neovascular leakage and ultimately complete repair and preserve the neurosensory retina.

Our modern-day therapeutic approach to managing neovascular age-related macular degeneration (NVAMD) is overwhelmingly via anti-vascular endothelial growth factor (anti-VEGF) strategies [1-4]. There are at least two mechanisms in which these agents achieve therapeutic significance, namely, through their anti-angiogenic and anti-permeability effects. Although anti-angiogenesis has only recently joined our expanding lexicon in retinal therapeutics, in reality our approach to NVAMD has always been anti-angiogenic [5-14]. Therapeutic anti-angiogenesis has its foundations in the 1960s and 1970s when the excellent reverse optics of the human eye were first exploited to give high-quality reproducible images with relatively compact fundus cameras and routine clinical fundus fluorescein angiography (FFA) arrived [15,16]. Coupled with this was the development of commercially available photocoagulators such as the ruby laser in 1960 and the Xenon arc, first developed in Essen, Germany, in the 1940s [17,18]. These three breakthrough developments of photography, angiography, and photocoagulation led for the first time to an expanding, albeit anecdotal, database of clinical evidence that supported anti-angiogenesis through vascular photocoagulation as a sight-saving therapy, observations that were initially seen in managing proliferative diabetic retinopathy (PDR). Thus, therapeutic anti-angiogenesis became a reality, and the targeted destruction, both direct and indirect, of abnormal blood vessels became the strategic goal of therapy for PDR and subsequently NVAMD. These initial clinical observations gave birth to the groundbreaking randomized control trials (RCTs) so familiar to present-day retinal specialists: the Diabetic Retinopathy Studies (DRS), the Early Treatment Diabetic Retinopathy Studies (ETDRS), and the Macular Photocoagulation Studies (MPS), which demonstrated for the first time that disease progression could be modified and sight saved [19-21]. These initial clinical observations and innovations led to the era of modern-day anti-angiogenesis.

However, technological advances rather than an appreciation of the underlying pathogenesis of disease conspired in this vascular-only approach to therapy, arguably at the expense of the "whole" picture of the underlying disease. This of course is wholly understandable as these early

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retinal pioneers strove admirably to deal with these visually devastating conditions as the race began to halt sight loss and refine this vascular-only therapeutic approach. NVAMD is one such maculopathy that demonstrates that its pathology embraces more than just a vascular component. Even if we are to continue just targeting this single aspect, then strategies other than pure anti-angiogenesis can and should be considered. These first retinal RCTs also confirmed FFA as a pivotal investigative tool in our approach to these conditions and reinforced therapeutic anti-angiogenesis [22]. Historically, FFA was perhaps unique as an investigation in that it became the surrogate of chorioretinal disease rather than what it actually was: a clinical investigation such that angiographic interpretation rather than pathobiology continued to dictate our approach to treatment. Fifty years on, FFA retains a central role in the diagnosis of AMD but has largely been superseded by ocular coherence tomography (OCT) in terms of ongoing management [23]. This review describes the rationale for considering treatments other than anti-angiogenesis by highlighting our improved understanding of what actually constitutes AMD, the role of chronic inflammation in triggering aberrant repair, and why current therapies are prohypoxic and thus only propagate the condition in the long-term.

## DISCUSSION

At the most fundamental, NVAMD appears to be an aberrant and stereotypical tissue repair response analogous to that occurring in skin, the tissue most commonly studied to define normal and abnormal healing responses [24-32]. Moreover, this assertion has been backed up in recent years with the recognition of the crucial role played by chronic inflammation in AMD [33-37]. From a tissue repair perspective, this role is not surprising. By definition, to generate any kind of inflammation, we require an injury. This is essentially the crucial step in activating a tissue repair response [31]. Ultimately, the nature of the reparative response generated depends on whether this insult is acute or chronic. In the case of acute injury, this could be a skin laceration such as a surgical incision, and the trigger for repair would appear to be the acute onset of local tissue hypoxia induced by the incision resulting from damage to blood vessels. This in turn generates acute inflammation and activation of the healing cascade leading to prompt and complete repair [31].

In the case of chronic diseases such as AMD, however, the initial insult can be insidious, persistent, and more difficult to define or identify. Where AMD is concerned, it has been suggested that it is dysregulated para-inflammation occurring in the aging eye that ultimately leads to chronic inflammation and in turn a chronic wound healing environment, which, by definition, is an injured tissue bed that does not heal [37-39]. This sequence of dysfunctional events in chronic diseases gives rise to the actual disease state. AMD, with its now recognized association with chronic inflammation, satisfies the definition of a chronic wound triggered by a combination of as yet poorly understood environmental insult(s) in genetically susceptible individuals and gives rise to the phenotype we recognize as AMD [40]. It would appear that the net result of this process, regardless of the precise sequence of events, is vascular dropout within the choriocapillaris causing hypoxia. This in turn leads to NVAMD [41-44]. However, hypoxia itself may not be the actual stimulus for neovascularization and other mechanisms may be at play [45-47]. Moreover, hypoxia may not adequately explain the clinical phenotypes of AMD characterized by geographic atrophy (GA) or CNV occurring within an area of GA. These phenotypes also tend to suggest that molecular components other than hypoxia, as advocated here, may be involved in the overall pathobiology of AMD. However, if AMD is considered from a wound healing perspective, the following hypothesis might be valid (Figure 1) [48]. Age-related hypoxia and ischemia of the outer macula including the retinal pigment epithelium (RPE) triggers oxidative stress and a secondary inflammatory response, itself part of the necessary response to generate healing. However, because the insult persists, the inflammation becomes chronic and increasingly amplified over years or even decades as the outer macula becomes even more hypoxic. We recognize this clinically by the appearance of drusen and pigment changes in the macula as the stressed retinal pigment epithelium, attempting to cope in this hostile environment, becomes increasingly dysfunctional. Eventually, the hypoxia becomes so profound that a neovascular response from the choriocapillaris is triggered, which we recognize clinically as CNV. In other words, this CNV is the expected neovascular component of the predictable stereotypical wound healing response referred to above [24]. However, because the entire process of repair has been aberrant, there is excessive recruitment of scar tissue that ultimately leads to permanent vision loss from the irreversible destruction of photoreceptors, so-called disciform scar formation [49].

Fundamentally, repair has occurred albeit with a pathological outcome. The same response occurring in the skin is necessary to close wounds to prevent or limit infection, restore function, and ultimately preserve life. Thus, where the skin is concerned, the neovascular component of repair is necessary to cause skin closure. Interference with this neovascular process in the skin such as occurs in diabetes or venous stasis generates ulcer formation; thus, healing is retarded or will not occur without intervention [50-56]. In the case of the macula, this tissue repair response is clearly

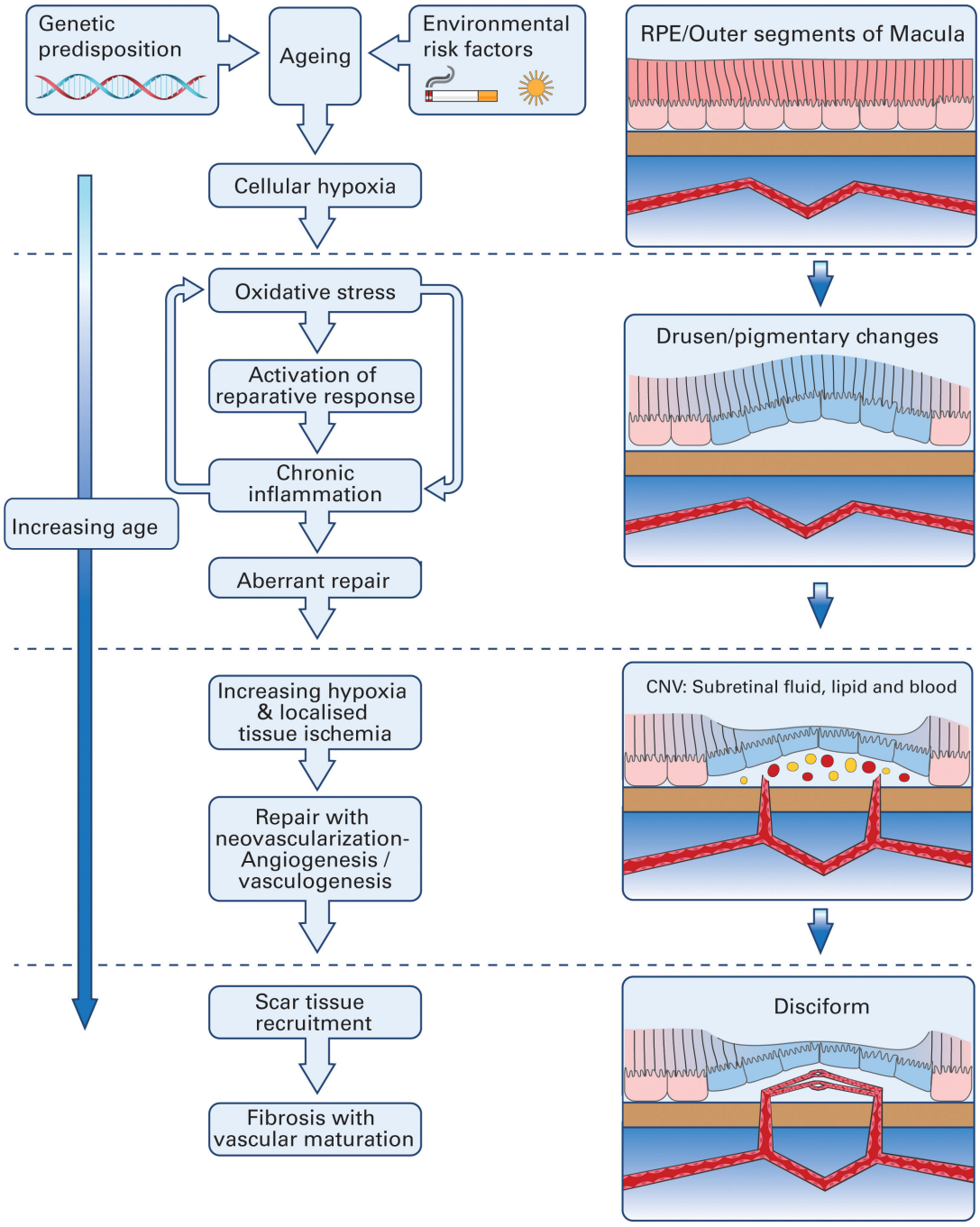


Figure 1. Temporal sequence of postulated development of age-related macular degeneration from a tissue repair perspective. CNV=choroidal neovascularization.

aberrant since loss of central vision ensues. However, if we at least acknowledge that the response by the body is an attempt at repair and that neovascularization or CNV is essential for this repair, then it would seem intuitive that at least one therapeutic challenge going forward is to complete repair without destruction of the outer retina and thus preserve vision. Perhaps from an evolutionary perspective, a disease containment response in the form of a disciform scar with loss of central vision is a price worth paying so that at least peripheral vision is preserved, and thus, the ability to navigate independently is maintained. Devising strategies other than anti-angiogenesis that could counteract this profibrotic state seems a reasonable goal of therapy [57]. In the first instance, and based on the assumption that this requires an adequate

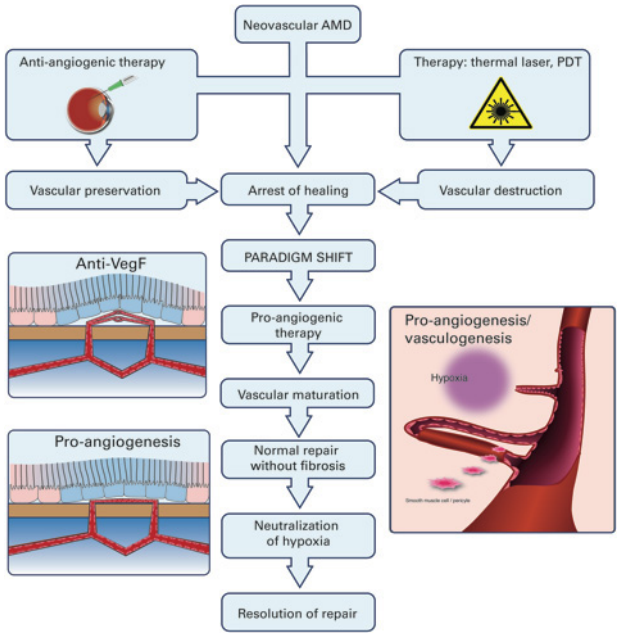


Figure 2. Therapeutic intervention for neovascular age-related macular degeneration from a tissue repair perspective. Complete repair requires an adequate blood supply. Our current approach leads to arrest of repair secondary to vascular destruction or compromise of vascular growth and therefore the inability of the macula to progress through the normal stages to repair for complete healing. Pro-angiogenic and vasculogenic strategies lead to accelerated neovascular maturation, cessation of vascular leakage, resolution of hypoxia, and prevention of excessive fibrosis to ultimately preserve photoreceptors and maintain vision. PDT=photodynamic therapy.

blood supply, it seems reasonable to suggest that this probably requires the preservation of the neovessels (CNV). In essence, all anti-angiogenesis achieves is arrest of repair, thus further fueling the ischemic response and preserving or even enhancing the hypoxic environment that triggered AMD in the first instance (Figure 2).

Before intravitreal therapy (IVT) was developed, our clinical experience bore this out. If we revisit the Macular Photocoagulation Studies data, we note such angiographic terms as "recurrence" or "persistence" of CNV, meaning that as defined by angiographic interpretation at the 6-week follow-up post-laser treatment, the neovascularization has either initially resolved and regrown (recurrence) or never fully resolved in the first place (persistence) [14]. Neovascularization, in the context of a wound healing response, has itself occurred in response to a hypoxic deficit (remember new vessel formation is but one component of a tissue repair response), and in the case of the Macular Photocoagulation Studies, thermal photocoagulation was applied to destroy the neovascular tissue making the retina/choroid tissue even more hypoxic. In this case, it is an acute, not a chronic, insult delivered by the laser, and therefore, rapid neovascular growth or regrowth occurs, all as nature intended. In other words, a further reparative response, including neovascular tissue formation, is initiated leading to recurrence or persistence of the neovascularization we recognize clinically. In cases where this does not occur, particularly in relation to the fovea, we often note clinically and on OCT that the vision is poor because of atrophic retina secondary to the AMD or scar "expansion" [58]. Thus, there is no hypoxic deficit to reactivate a wound healing response. In addition, in lesions that are extrafoveal or juxtafoveal, we note that the recurrence almost always occurs on the foveal side of the laser photocoagulation scar, again supporting the concept of the increased metabolic demand in the fovea compared to other neurosensory retina (NSR) elements and thus where the potential hypoxic deficit is maximal [59-63]. The same can be said of photodynamic therapy (PDT) with verteporfin, a "cold" laser that photoactivates a dye that is preferentially taken up by endothelial cells in neovascular tissue [64]. The photoactivated dye then causes destruction of these endothelial cells by generating reactive oxygen species [65]. However, based on our hypothesis, PDT will have generated further hypoxia and therefore generation of an expected tissue repair response that ultimately leads to reperfusion of CNV or indeed further NV growth and thus the need for retreatment [10,66].

It thus seems that our anti-angiogenic approach is counterproductive in the long-term and that perhaps our therapeutic strategy should not be so much about vascular destruction as at the very least vascular tolerance until we develop more scientifically appropriate therapies that address early symptomatic or even asymptomatic stages of non-NVAMD. Yet, almost by default, PDT and especially IVT permit a primitive form of vascular tolerance. Although our current goal might remain vascular destruction, vascular containment seems more appropriate, and this has, of course, demonstrated huge benefits in terms of visual preservation as there appears to be none or little compromise or destruction

of the overlying NSR. However, the downside is the number of injections required per eye to sustain vision. At the time of writing, this will usually mean ongoing therapy for life. IVT has also demonstrated that vision preservation is not necessarily about new blood vessels and their destruction but instead about "leakage" from the blood vessels. In modern parlance, this leakage is the new "recurrence" and thus a clinical indicator of the need for further treatment [67]. Control the "leakage," and you preserve or improve the vision. Thus, it is more appropriate to refer to this therapy as anti-inflammatory or anti-permeability rather than anti-angiogenic, bearing in mind that VEGF has also been termed vasopermeability factor (VPF) and is a potent mediator of inflammation in wound healing. Perhaps this anti-inflammatory property is more therapeutic in relation to drying up the macula and preserving photoreceptor function [68,69]. Furthermore, and in keeping with the tissue repair theme, histologically CNV demonstrates a temporal maturation of all essential components, including vascular maturation evolving from fine capillary vessels to more stable vascular structures and may be refractory or poorly responsive to anti-angiogenic agents [70], again supporting the notion that the therapeutic effect is anti-inflammatory or anti-permeability. This of course begs the question whether we should be looking at more novel agents that are solely anti-inflammatory even in the comparatively advanced stage that is NVAMD. This would permit vascular maturation to occur as there would be no coexisting anti-angiogenic action by such an agent.

The role of aging in AMD is also important. In younger patients with CNV (myopia, trauma, and uveitis), the lesion complex tends to be smaller, scar tissue recruitment is less, and resolution of disease is more rapid, suggesting that regardless of etiology and the fact that final central vision loss can be profound, a more efficient inflammatory process and by implication the repair mechanism is at work [71-75]. In the absence of an effective therapy for non-NVAMD, the challenge in the future has to be about modifying the chronicity of the NVAMD lesion complex. Further compromise of the blood supply via anti-angiogenesis will only propagate this chronicity and promote recurrence and reparative arrest [76]. The importance of renewing or improving blood supply is seen firsthand in several systemic conditions that are managed by pro-angiogenic strategies. Bypass grafting, in coronary heart and peripheral vascular disease, carotid endarterectomies, and of course the use of stents in more recent years are all indicated for vascular pathology underpinned by chronic inflammation [77-84]. In addition, the use of exercise in promoting collateral blood vessel formation similarly highlights the importance of maintaining or enhancing blood supply in ischemia, with the exception of oncologists who understandably want to limit tumor growth by compromising the tumor's ability to recruit a blood supply. However, even in oncology an anti-angiogenic approach may be misguided due to the promotion of even greater hypoxia and inflammation in the tumor bed and the implication that this has on overall patient prognosis and survival [85,86].

The emphasis on this single neovascular aspect of CNV has also had implications for scientific research. We have many models of NVAMD, all of them imperfect but nevertheless leading to many scientific discoveries. However, almost all of them are underpinned by the drive for more anti-angiogenic therapeutic strategies. One such model is the "laser to Bruch's membrane" now chiefly used in the rodent though first developed in the primate [87,88]. This model is an excellent proof of principle model albeit for two different reasons. First, if we rupture Bruch's membrane, this model demonstrates neovascular in-growth into the subretinal space, analogous to that seen in NVAMD. Second, if one wants to test a therapeutic agent to prevent or retard this in-growth, this model is also ideal. In reality, it is probably more accurate to describe this model as an excellent example of acute wound healing and what occurs when one delivers an acute laser injury to the back of the eye [24]. From an AMD and anti-angiogenic perspective, this model is probably overused, as it is not a good model of chronic disease. Furthermore, the laser is an acute insult in a young mouse (as opposed to the chronic inflammatory insult of AMD in an aging human) and generates an acute inflammatory reaction. Therefore, this milieu is ideal for repair to progress through the coordinated series of phases to wound resolution [31,76]. Extrapolating the results of a potential therapy from this acute model to the reality of a diseased and aging human retina is not ideal. However, accepting these limitations, this preliminary model may be useful for investigating other aspects of the lesion complex and their potential therapies, including inflammation, scar tissue recruitment, natural history, and end stage disease without interfering with the neovascular process. Finally, this model could also provide an initial template for studying vascular maturation in the context of NVAMD.

If IVT has demonstrated that we can tolerate CNV (at the expense of reparative arrest), then the next step perhaps is to consider treatments that may stimulate or accelerate vascular maturation vis-à-vis vascular remodeling, investment with pericytes, and deposition of basement membrane as well as the role of vasculogenesis and the use of cell therapy in this process [26,89-93]. Such vascular tolerance in combination with a promaturation matrix could reduce "leakage," push repair toward completion, and ultimately preserve vision. In end stage untreated or treatment failure NVAMD, these

mature vessels can often be visualized clinically and can demonstrate vascular maturation and competence angiographically and histologically [49,94]. Retinal angiomatous proliferation (RAP) may also represent a primitive or aberrant form of attempted repair in NVAMD as the vascular component of these lesions seems to represent various states of maturation that would again satisfy the definition of repair, that is, vascularization of a pro-angiogenic matrix [95-99].

An alternative hypothesis may support the use of anti-angiogenic therapy in NVAMD but in combination with therapies that promote vascular maturation and remodeling (Figure 2). In ischemia that occurs in the heart or brain, an initial hypoxia-induced acute vascular response can lead to further tissue damage due to the vasopermeability effect of VEGF causing tissue edema [68,100]. Inhibiting this VEGF effect could be therapeutically beneficial [101]. Once over the acute phase, there is the delayed phase of tissue ischemia, where stimulation, formation, maturation, and remodeling of vascular networks should promote long-term functional improvement. The merits of such a pro-angiogenic approach could be directly applicable to not only NVAMD but also non-NVAMD when one considers the postulated association between vascular dropout within the choriocapillaris and the pathogenesis of AMD [43,44]. Growth factors such as platelet-derived growth factor (PDGF), the angiopoietins (Ang), and hepatocyte growth factor (HGF) promote these different components of vascular maturation and therefore may have a role to play in promoting tissue repair in NVAMD [102-104]. Ultimately, from a wound healing perspective, combination therapy may provide a realistic and sustained benefit in the future.

In conclusion, in the absence of any effective therapy for non-NVAMD, our current therapeutic armamentarium for CNV is directly or indirectly anti-angiogenic. This approach was originally founded on the principle that blood vessels could be imaged, identified, and then thermo-ablated with laser. Eventually, this approach of neovascular intolerance gave way, initially to PDT and more recently to IVT and the evolution of a more vascular-tolerant approach. In reality, AMD, like all acquired pathologies, is a chronic disease underpinned by chronic inflammation thus creating the permissive environment that ultimately can lead to aberrant submacular repair, scar tissue recruitment, and irreversible vision loss. What we recognize clinically as CNV is the neovascular component of this reparative response. In such a situation, IVT, although undoubtedly beneficial in terms of visual preservation, propagates the hypoxic environment leading to potential reparative arrest or even a profibrotic state; thus, repeated therapy is required. Conversely, it aptly demonstrates for the first time that clinically we can tolerate the presence of neovascular tissue in the submacular space and still preserve or improve vision. This juncture in the evolution of our current understanding of CNV raises a genuine therapeutic dilemma and begs the question whether now is the time to take the "anti" out of angiogenesis and instead advocate therapies that promote disease resolution by supporting vascular maturation and essentially what we might term proangiogenic therapy.

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