Hypothesis

A hypothetical therapeutic effect of light peripheral panretinal photocoagulation in neovascular age-related macular degeneration

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ABSTRACT

Background: Vascular endothelial growth factor (VEGF) is a significant modulator of ocular angiogenesis, including that of neovascular age-related macular degeneration (nAMD). Intravitreal injection of anti-VEGF is the benchmark treatment for most retinal vascular diseases, including nAMD, diabetic maculopathy, and macular edema secondary to retinal venous occlusion. Anti-VEGF treatment is a high-frequency, time-consuming, non-cost-effective therapy, especially in countries and regions with limited resources. This treatment is easily restricted, and in practice, maintaining long-term periodic care is challenging for patients.

Hypothesis: Light peripheral panretinal photocoagulation (PPRP) is applied in a mild form (barely visible mild light gray mark) anterior to the equator so as not to jeopardize the visual field. PPRP lessens the ischemia that causes neovascularization and decreases the metabolic demand in the peripheral retina. PPRP reduces serum angiopoietin-2 and VEGF levels in patients with type 2 diabetes mellitus with proliferative diabetic retinopathy. We propose using light PPRP to suppress VEGF secretion, aiming to attenuate the VEGF drive and halt choroidal neovascular growth in eyes with nAMD. Our regimen is based on two concepts: first, nAMD is a diffuse or generalized disease that affects the posterior segment; and second, PPRP is very effective in regressing diabetic retinopathy. PPRP has reportedly been successful in cases of macular edema (diabetic or following venous occlusion) resistant to VEGF antagonists. Light PPRP may be used as prophylaxis, adjunctive treatment, or monotherapy in nAMD when intravitreal injections of VEGF antagonists are not feasible.

Conclusions: The established light PPRP therapy could be promising as a one-time, cost-effective therapy or prophylaxis in patients with nAMD or at high risk. This proposed modality could be suitable for patients who have injection phobia or prefer a one-time affordable therapy to the long-term monthly visits to retinologists. Future trials are necessary to verify the safety and efficacy of this proposed treatment modality in selected patients with nAMD.

KEYWORDS

age related macular degeneration, wet macular degeneration, laser therapies, VEGFs, vascular endothelial growth factors, choroid neovascularization, retina

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INTRODUCTION

Neovascular age-related macular degeneration (nAMD) associated with choroidal neovascularization (CNV) is a multifactorial, multi-genetic disease [1] and a dominant cause of visual impairment among persons aged over 50 years. There is currently neither a cure for nAMD [1] nor a reliable preventive measure. However, if left untreated, nAMD will progress to a disciform scar, causing severe loss of vision [1].

Intravitreal vascular endothelial growth factor (VEGF) antagonists have transformed therapy for nAMD [2]. The transient nature of the therapy requires a prolonged course of serial injections (Figure 1) and produces limited durable restoration of visual acuity. An extended hiatus in ophthalmic management, which is highly likely, may result in irreversible visual loss [3, 4]. Some patients experience high anxiety levels [5] and even panic attacks during the procedure and become averse to such interventions. The high cost, inconsistent compliance, and inconvenience issues limit injection therapies. This is most evident in many third-world countries; the costs of approved anti-VEGF biologic therapies, medical care, and transportation can be prohibitive [6].

Alternatives that combine single treatment, affordability, and avoidance of frequent follow-up would best fit many patients, especially those reluctant to have a needle puncture the eye. If our goal is to suppress intraocular VEGF levels using such injections, a possible alternative is to decrease the VEGF level using light peripheral panretinal photocoagulation (PPRP) [7].

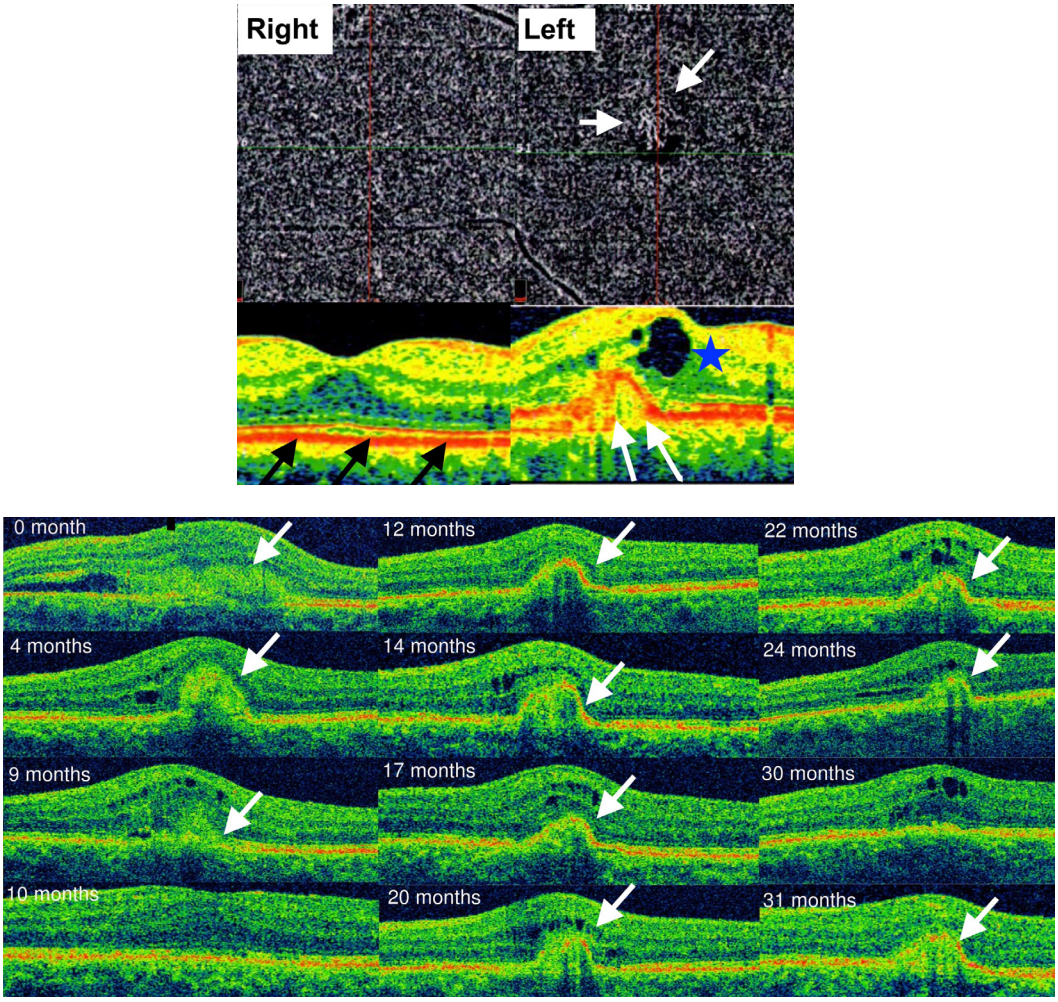

Figure 1. Optical coherence tomography (OCT) angiography of the superficial choroid (top composite) and 12 serial horizontal OCT scans through the macula (bottom composite) of this 83-year-old Caucasian man who received 33 injections of ziv-aflibercept (Zaltrap; Sanofi-Aventis, Paris, France) over 32 months of follow-up. He required monthly injections to control the choroidal neovascularization (white arrows on OCT and OCT angiography of the superficial choroid) in the left macula with breaks in Bruch's membrane (2 white arrows). Cystoid macular edema is noted by a blue star. Subretinal hemorrhage at presentation resulted in the loss of central vision, but vision recovered to 20/25. Monthly eye exams, OCT scans, and intravitreal injections resulted in the restoration of vision.

Table 1. Proposed criteria for selection of patients with nAMD for light peripheral panretinal photocoagulation

Potential candidates
Fellow eye in patients with active CNV (drusen and dry AMD) [13, 14].
High-risk AMD, soft drusen in patients unable to be closely followed [15, 16].
Active CNV in patients averse to intravitreal injections (patient unwillingness) [17].
Active CNV in patients unable to afford intravitreal injections [18-20].
Active CNV in patients wishing to discontinue current intravitreal therapy [15, 18, 20-22].

Abbreviations: nAMD, neovascular age-related macular degeneration; CNV, choroidal neovascularization; AMD, age-related macular degeneration.

HYPOTHESIS

The molecular and physiological mechanisms of angiogenesis involve the successive activation of receptors by several growth factors, most importantly VEGF [8]. VEGF acts as both a growth and a survival factor in target tissues, promoting angiogenesis by inducing mitosis and swelling of retinal vascular endothelial cells [9]. Although hypoxia is the most prevalent factor in the induction of VEGF synthesis, molecules linked to inflammatory conditions within the eye can increase VEGF messenger RNA synthesis [10]. Although VEGF influences various retinal cells, vascular endothelial cells are its main target [9]. VEGF is the canonical angiogenic signaling molecule and biomarker of nAMD [8, 9]. VEGF is released by retinal neurons, glia, and vascular endothelial cells, but mostly by retinal pigment epithelium (RPE) [8].

Suppression of VEGF secretion is achieved by intravitreal injection of VEGF antagonists or by ablation of the RPE using laser therapy [9]. As of June 2022, VEGF antagonists that are clinically available include bevacizumab, ranibizumab, aflibercept, ziv-aflibercept, brolucizumab, conbercept, faricimab, and two biosimilars (ranibizumab-nuna [Byooviz™] and ranibizumab [Susvimo™]) [10]. Because of the short half-life of these medicines, frequent injections of intravitreal VEGF antagonists represent the standard of care in nAMD [2].

Light laser therapy [7] is proposed as a unique, innovative strategy to significantly lower VEGF secretion in nAMD, as both therapeutic and prophylactic measures. Light PPRP is the designation given to this laser treatment [7]. PPRP is applied in a mild form (barely visible mild light gray mark) [7, 11] anterior to the equator so as not to jeopardize the visual field [11]. PPRP lessens the ischemia that causes neovascularization and decreases metabolic demand in the peripheral retina [12].

Herein, the authors hypothesize that using light PPRP may reduce the VEGF load to a level that is inadequate for CNV formation after peripheral VEGF is suppressed. This method can potentially be used for naive nAMD, nAMD after previous injections, and preventive treatment in fellow eyes of patients with nAMD. The laser may at minimum reduce the number of injections required for durable management of neovascularization in situations when nAMD activity is lessened but not controlled. Our proposed criteria for patient selection are listed in Table 1.

EVALUATION OF THE HYPOTHESIS

nAMD does not represent a localized disease of the posterior pole; rather, it reflects a more generalized or diffuse change [23-25]. The associated peripheral lesions (drusen, pigmentary changes, or atrophy) were discovered in 82.7% of AMD-affected eyes compared to 33.3% of healthy eyes in a meta-analysis [25].

PPRP of the periphery of retina is not unique to nAMD. PPRP has been suggested in diabetic maculopathy [9, 26] and macular edema related to retinal venous occlusion [27, 28], and is the benchmark therapy for retinopathy of prematurity [29] and proliferative diabetic retinopathy (PDR) [12]. In PDR, PPRP appears to lower intraocular and plasma VEGF concentrations and to result in regression of ocular neovascularization [30-33]. In eyes with PDR, the aqueous level of VEGF significantly decreased as the extent of PPRP increased and had a significant correlation with total PPRP [34]. Similarly, intraocular VEGF levels are elevated in nAMD [35] to levels quite similar to or less than those in diabetic retinopathy [30, 36]. If the same laser approach is used in nAMD, we may expect similar yet more moderate VEGF suppression.

Laser PPRP is intended to lower intraocular VEGF levels, leading to prophylaxis, growth arrest, or eventual regression of CNV. Ichiyama et al. [37] and Minaker et al. [38] observed that aqueous VEGF levels were increased in active nAMD and that these levels markedly decreased following intravitreal anti-VEGF injections [39]. After PPRP, many proinflammatory cytokines are reduced [33]. The aqueous levels of several proinflammatory cytokines, including transforming growth factor β1 (TGF-β1), were markedly reduced in diabetic eyes after PPRP compared to those before PPRP [33]. Increased levels of angiopoietin-2 in the vitreous fluid of patients

with PDR suggest an association of angiopoietin-2 and VEGF with angiogenic activity in PDR [40]. PPRP reduced serum angiopoietin-2 and VEGF levels in patients with type 2 diabetes mellitus and PDR [41].

Consequences of the Hypothesis

In one study, approximately 22% of patients with nAMD that were treated with VEGF antagonists were lost to follow-up [15], and this may lead to irreversible visual loss [42]. In a single facility, 2003 (22.2%) of 9007 patients examined over 4 years were lost to follow-up [15]. The likelihood of being lost to follow-up heightens with increasing age, low socioeconomic status, and increasing distance from the medical facility [15]. Besides the loss to follow-up, lapses in medical care can reach 50% in eyes that require frequent intravitreal injections over a follow-up of 5 years [3, 4].

Here, we are referring to selected patients that (1) refuse injections into the eye (injection phobia) [20, 43], (2) cannot afford the continual repeated examinations and injection costs (low socioeconomic status) [20, 44], (3) have comorbidities [20, 44, 45] requiring repeated admissions for medical or surgical purposes (e.g., fractures, strokes, myocardial infarctions, malignancies, renal dialysis, and other diseases that take priority over ocular status), (4) have low health literacy [46], (5) are isolated with a lack of support and resources to orchestrate their transport to regular appointments [47], and finally (6) have altered mental status due to Alzheimer disease [45] or uremic encephalopathy.

When determining the optimal treatment for a patient who requires frequent intravitreal injections, factors such as practicality, compliance, and cost must be considered [4, 6]. A study of PDR showed that PPRP provided good control for a minimum of 15 years [48]. Anti-VEGF therapy, on the contrary, is intensive and necessitates regular monitoring. The length and frequency of anti-VEGF injection therapy are frequently unclear, and the prolonged and seemingly never-ending regimen occasionally exasperates patients [4, 6, 15, 42, 49, 50] (Figure 1).

One Markov-style model of health care costs found that PPRP is more cost-effective than intravitreal ranibizumab in treating PDR [49]. We estimated considerable cost savings over 15 years (Table 2) [2, 3, 6, 9, 10, 39, 49, 50]. However, a cost-effectiveness analysis [51] to estimate the economic efficiency of this proposed treatment modality in eyes with nAMD is required.

Role of VEGF in nAMD

VEGF antagonists clearly and significantly affect how CNV is managed in nAMD [50, 52-59]. It is not yet clear how RPE cells are stimulated to release VEGF, leading to CNV formation and growth [8, 28, 52, 53]. Studies of CNV in patients with nAMD and animal models of nAMD have demonstrated the presence of various angiogenic factors, including VEGF [54].

The retina receives oxygen from two different circulatory systems. While the inner retina receives its oxygen from the retinal circulation, which travels through the inner retina, the choroid supplies the oxygen needed for the outer retina [10]. There is a substantial oxygen gradient towards the inner segments of the photoreceptors, which have the highest oxygen requirement, whereas the choroid has the highest oxygen levels [12].

Disturbances in oxygen diffusion from the choroid result from an increased distance from the choriocapillaris to the retina. This anatomic barrier is the result of drusen formation, RPE detachment, thickened Bruch's membrane, subretinal fluid, exudates, or hemorrhages [52-54]. Because the demand for

Table 2. Differences between current standard therapy and proposed light PPRP for nAMD

Parameters	Biologic VEGF blockade	Light PPRP
Effect	Transient (1 to 2 months) [3]	Long-term (> 15 years) [48, 49]
Number of sessions	Multiple [50] 52.2 injections over 10 years	Single [48]
Intensity	Monthly, then bimonthly, then as needed, or treat and extend [2, 10, 39]	Once [15]
Close follow-up	Extended monthly 58.3% have ongoing treatment at 10 years [50]	As needed
Cost (exam, OCT imaging, procedure, medication, transportation)	+++ [6, 10]	+ [9]
Endophthalmitis	+ (rare) [2]	No
Thromboembolic events	+ (rare) [2]	No

Abbreviations: PRRR, peripheral panretinal photocoagulation; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor; OCT, optical coherence tomography.

oxygen in the outer retina is high, and oxygen cannot be stored, a continuous supply is essential. A drop in the oxygen flux to the photoreceptors would not meet the needs of the rods and cones, resulting in ischemia and increased VEGF production [55-57].

Molecular factors secreted by retinal microglia and the RPE generate a micromilieu that is favorable for VEGF-driven CNV, even if the ischemic drive in nAMD is not quite as severe as in diabetic retinopathy [35, 36, 55, 56]. VEGF overexpression by the RPE also enhances the effects of increased oxidative stress and low-grade inflammation [58, 59]. Recently, complement pathways were shown to regulate the genesis of CNV [56]. Additionally, there is experimental evidence for the role of activated macrophages in inducing CNV in one animal model of nAMD and patients with advanced nAMD [58].

How does PPRP work?

The following steps demonstrate the mode of operation of PPRP. The laser energy is absorbed by the melanin granules inside the RPE. The surrounding photoreceptors are destroyed and are replaced by a thinner glial scar, resulting in decreased oxygen consumption [12, 52]. As a result of this oxygen diversion, the surrounding outer retina is no longer hypoxic, and oxygen tension around the scar is increased [12, 52]. Relief from hypoxia reduces the synthesis of growth factors such as VEGF and facilitates the regression of retinal neovascularization [12]. However, further clinical trials are needed to verify the safety and efficacy of light PPRP in selected patients with nAMD.

CONCLUSIONS

The authors propose light PPRP as a novel therapy for nAMD. Because of the anatomic barrier between the RPE and the choroid in nAMD, which limits oxygen flux and results in ischemia, the RPE is stimulated to release VEGF. Through the laser scars, where oxygen consumption is minimal, the neighboring RPE, photoreceptors, and inner retinal layers achieve an increase in oxygen flux, resulting in VEGF suppression and control of CNV. Our proposed regimen may be used as prophylaxis, adjunctive treatment, or monotherapy in nAMD when intravitreal injections of VEGF antagonists are not feasible. This proposed modality is suited for patients who have injection phobia or prefer a one-time affordable therapy rather than continuous monthly visits to retinologists. However, cost-effectiveness analyses and clinical trials will be required to estimate the economic efficiency, safety, and efficacy of this proposed treatment modality for eyes with nAMD.

ETHICAL DECLARATIONS

Ethical approval: This is a theoretical hypothesis to propose light PPRP as a novel therapy for nAMD, and no ethical approval is required.

Conflict of interests: None

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