Context for Protons as Adjunctive Therapy in Neovascular Age-Related Macular Degeneration: A Review

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Abstract

In the last few years we have witnessed increasing availability of proton therapy in the United States and worldwide. As a result, proton therapy is considered as either a primary or adjunctive approach for numerous indications where conventional radiation therapy shows promise but is accompanied by toxicities. Age-related macular degeneration (AMD) remains the leading cause of adult blindness in industrialized nations, and third worldwide, following cataract and glaucoma. Current standard therapy is intravitreal injection of anti–vascular endothelial growth factor agents. While this treatment shows improvement and stabilization in visual acuity for 40% of patients, 60% still experience disease progression. These injections are costly, necessitate repeated office visits, and carry the risk of endophthalmitis. The pathophysiology underlying neovascular AMD (nAMD) underscores the need to simultaneously target multiple pathways to retain useful vision. Radiation can be antiangiogenic, anti-inflammatory, and antiproliferative. Early photon therapy clinical trials were heterogeneous, and a Cochrane review of data demonstrated usefulness in treatment of nAMD but recommended further studies. Advantages of proton therapy over photon therapy include the ability to deliver a focal dose to the target while minimizing dose to normal structures, which is enhanced by unique treatment planning software that uses fluorescein angiography to verify target location and allows conformation of dose to the irregular shape and thickness characteristic of choroidal neovascular membranes, the pathognomonic finding in nAMD. Preliminary data suggest a potential role for proton therapy in the treatment of nAMD. In this article we review previous treatments for AMD, including those with both photon and proton radiation, and recommend future directions for clinical investigations to evaluate the role of proton therapy as an adjunct to antiangiogenic therapy, the current standard of care in this challenging setting.

Keywords: age-related macular degeneration; protons; neovascularization

Introduction

Age-related macular degeneration (AMD) is the most common cause of adult blindness in developed countries and the third worldwide, following cataract and glaucoma [1]. Age-related macular degeneration involves the macula, a region of the retina responsible for facilitating central vision and high-resolution visual acuity (VA) [2]. The nonexudative variant of the disease is characterized by the presence of drusen, accumulations of
extracellular material between Bruch membrane and the retinal pigment epithelium (RPE) [3]. The exudative or neovascular variant of the disease, affecting 10% to 15% of patients, is defined by the presence of choroidal neovascularization (CNV) and abnormal vascular proliferation originating from the choroid, penetrating Bruch membrane and proliferating deep to the retina. Although neovascular AMD (nAMD) comprises a smaller proportion of AMD, it accounts for >80% of the severe visual loss or legal blindness attributable to AMD [4]. In 2010, AMD affected more than 2.07 million individuals in the United States and is expected to increase to 288 million worldwide by 2040, with almost 5.44 million in the United States by 2050 [5, 6].

Increasing availability of proton therapy has led to consideration of its use as either a primary or adjunctive approach in numerous indications, including nAMD, in which conventional external beam photon therapy has shown promise but has been limited by toxicity. Our review will focus on the history of treatment of nAMD with special attention to radiation therapy, and forethought to future trials to assess proton therapy as an adjunct to antiangiogenic therapy, the current standard of care.

**Historical Context**

**Diagnosis**

The diagnosis of nAMD is made by using multiple modalities: biomicroscopy, psychophysical testing, optical coherence tomography, indocyanine angiography, and fluorescein angiography (FA). Where biomicroscopy may pick up structural indicators of active neovascularization (eg, exudation, hemorrhage, edema, and fluid), psychophysical testing may reveal functional decline. Optical coherence tomography may be used to detect early edema or fluid too subtle to be observed biomicroscopically. Indocyanine angiography and FA may be used to elucidate the neovascular complexes themselves, as made evident by characteristic angiographic leakage. Fluorescein angiography and optical coherence tomography are the most commonly used imaging modalities for radiation treatment planning (**Figures 1 and 2**).

**Treatment Approaches**

**Dietary supplementation**

After epidemiologic evidence showed decreased risk of nAMD with higher serum concentrations of carotenoids and antioxidants [7–9], the Age-Related Eye Disease Study (AREDS) demonstrated a 25% decrease in conversion from intermediate to advanced nAMD with supplementation of β-carotene, vitamin C, vitamin E, and zinc at 5 years [10]. Although these supplements do not prevent the development of AMD, they are useful once AMD has developed to prevent further visual...
deterioration in a minority of patients [11, 12]. The AREDS2 study added lutein (10 mg) and zeaxanthin (2 mg) or docosahexaenoic acid (350 mg) plus eicosapentaenoic acid (650 mg) (or both) to the original AREDS formulation. While results were not superior to the original formulation, smokers would benefit more from this formulation, as β-carotene supplements have been linked to increased lung cancer risk in smokers, and the formulation in AREDS2 eliminates β-carotene [13].

Photocoagulation

Early treatment of CNV focused on photocoagulation with or without porphyrins. The Macular Photocoagulation Study compared 2 laser treatments (argon green and krypton red) for CNV in the extrafoveal, juxtafoveal, and subfoveal regions. The argon green laser trial of extrafoveal CNV (200–2500 μm from the center of the foveal avascular zone) showed 25% and 60% severe visual loss in treated and untreated patients, respectively [14]. However, 59% of treated patients developed recurrent neovascularization, often soon after treatment (24% at 6 months, 43% by 1 year) [15]. The krypton red laser study treated juxtafoveal CNV lesions with a posterior border 1 to 199 μm from the center of the foveal avascular zone. At 3 years, 49% and 58% of treated and untreated patients, respectively, lost ≥6 lines of VA (P = .02). Thirty-two percent of treated eyes had persistent neovascularization, and 47% developed recurrent neovascularization [16]. At 5 years, the relative risk of a loss of ≥6 lines between untreated and treated individuals was 1.20 (P = .04) [17]. Four-year outcomes for subfoveal treatment (randomly assigned to argon green or krypton red lasers) showed that 22% of patients with treatment-naïve CNV and 47% with recurrent CNV experienced a loss of ≥6 lines in VA from baseline (P = .002) [18]. The trade-off for this late improvement was early loss of VA (3 lines within 3 months of treatment), making this less than optimal for patients already presenting with visual compromise [19].

Photodynamic therapy

In photodynamic therapy a photosensitizing drug, verteporfin, is injected peripherally. It is then activated by a laser of a wavelength corresponding to peak absorption for verteporfin. This activation causes a destructive photochemical reaction specific to the vascular endothelium of the neovascular lesion. It is postulated that this reaction manifests its effect via a combination of free radical creation, oxidative damage, and vascular thrombosis. In the verteporfin study [20] those treated
fared better than the control population, with 47% of treated eyes and 62% of controls losing >15 letters (or 3 lines) of VA ($P < 0.001$) [21]. Despite eventual VA stabilization, the initial loss of VA is significant and unacceptable to many patients. The use of photodynamic therapy has decreased since the increased use of anti–vascular endothelial growth factor (VEGF) therapy.

**Antiangiogenic therapy**

Presently, antiangiogenics, therapeutic agents targeting VEGF, predominate in the treatment of CNV. These agents improve vision in up to 40% of cases; note that prior therapeutic modalities were aimed at visual “stability” [20, 22]. The US Food and Drug Administration (FDA) approved pegaptanib sodium, a pegylated anti-VEGF aptamer that binds to the 165 isoform of VEGF, for the treatment of nAMD in 2004 [23]. Ranibizumab, an antibody fragment from the same parent molecule used for synthesizing bevacizumab, was demonstrated both to yield visual improvement [23] and to be superior to photodynamic therapy [20]. Bevacizumab, a full-length humanized monoclonal antibody to VEGF-A, originally FDA-approved for treatment of metastatic colorectal cancer in 2004 [24], was initially given off-label approval for nAMD [25], showing improvement of CNV with concurrent reduced retinal thickening and improved VA. These results, originally observed with intravenous administration, were reproduced with intravitreal administration [26, 27]. The US Comparisons of AMD Treatments (CATT) [28, 29] and the UK Inhibition of VEGF in Age-Related CNV (IVAN) trials [30, 31] were head-to-head comparisons of intravitreal bevacizumab and ranibizumab that showed noninferiority of bevacizumab and have supported off-label use of bevacizumab for AMD as a cost-effective alternative to ranibizumab. Most recently, aflibercept, a recombinant fusion protein that competes for binding of circulating VEGF, was approved by the FDA and has subsequently been found to be equivalent to ranibizumab, but it has not been tested head-to-head with bevacizumab in clinical trials [32, 33]. Randomized trials with long-term data are available for intravitreal ranibizumab [34] and comparing intravitreal bevacizumab with ranibizumab [30, 35]. Pegaptanib is less effective than bevacizumab or ranibizumab and is therefore infrequently used [36].

Polymorphisms in the complement factor H gene predispose individuals to developing AMD through increased inflammation resulting from abnormal regulation of the alternative complement pathway [37–42]. Histopathologic analysis of patients treated with anti-VEGF agents reveals that the bulk of residual tissue is avascular subretinal fibrosis, which can grow and impede vision. Further, antiangiogenic therapy necessitates monthly intraocular injections that are costly, burdensome to the patient, and expose the patient to risk, repeatedly. Given the societal cost of this disease, along with wider understanding of its pathogenesis, multiple biochemical pathways must simultaneously be targeted to improve outcomes.

**Rationale for Radiation Therapy**

Ionizing radiation is known to have dramatic effects on blood vessels through creation of reactive oxygen species and DNA single- and double-strand breaks, especially in endothelial cells, and also acts to inhibit hyperproliferative processes such as keloids, and hypertrophic osteoarthropathy [43, 44]. Rabbit eyes focally irradiated with 60Co ophthalmic plaques show delayed and attenuated inflammatory and repair responses and decreased granulation tissue [45]. In addition, eyes treated with low-dose radiation for CNV show decreased proliferative fibrosis and scarring, compared with untreated eyes, as well as better maintenance of VA [46]. These effects would be expected to halt the progression of nAMD [47, 48], but for appropriate clinical efficacy, retention of VA is a necessity. The ability of highly focal ionizing radiation to retard the growth of new blood vessels and at the same time spare vision suggests a possible therapeutic role in treatment of CNV.

**Early Experience with External-Beam Radiation Therapy**

A pilot study of 19 patients with CNV treated with external-beam radiation therapy (EBRT) to a dose of 10 to 15 Gy showed maintenance of central acuity and regression of CNV [49]. Visual acuity was maintained or improved in 63% and 73% of patients at 12 and 18 months, respectively. Visual acuity decreased in 6 of 7 untreated patients. Fluorescein angiography showed significant or complete CNV regression in 83% and 91% of patients at 12 and 18 months, respectively, after treatment. All controls ($n = 7$) showed progression by 12 months.

These results prompted several phase I/II studies evaluating external-beam photon therapy for CNV [50–65]. Trial designs were heterogeneous, limiting comparisons and conclusions. In addition, follow-up periods in most of these reports were quite short, with most reporting results 6 to 12 months after treatment; further, only 2 studies included control populations [60, 61]. Pooled analyses of these phase I/II trials ($n = 409$) showed that 22.5% and 14.9% of EBRT-treated eyes developed moderate and severe loss of vision, respectively—an ~50% reduction in the anticipated natural progression of the disease [66].
Eleven prospective phase III randomized controlled trials followed [67–77]. Findings from these trials were inconsistent with regard to VA and CNV membrane size. Two of the 11 trials [71, 72] showed significant stabilization/improvement in both VA and CNV size, whereas significant stabilization/improvement in VA alone was found in 3 of the trials [68, 69, 77] and CNV size regression or contrast sensitivity alone was preserved in 2 trials [75, 76]. Six of the 11 randomized trials [67, 70, 73–76] failed to identify any benefit. Two studies [68, 69] showed hypofractionation (given in 6 and 7.5 Gy per fraction) to be superior to conventional fractionation schema. A 2010 review [78], including 13 randomized trials (1 brachytherapy trial) and 1154 patients, showed a statistically significant reduction in risk of VA loss in the treatment group. Because of the relatively small magnitude of benefit, the authors recommended further trials with masked control groups to better characterize the role and value of EBRT for nAMD. In the trials reviewed, higher total doses of radiation, as well as hypofractionation schedules using higher dose per fraction, showed greater magnitudes of benefit.

**Brachytherapy Trials**

Traditional EBRT can deliver as much as 30% to 50% of the prescribed dose to the crystalline lens [49, 68]. To prevent unwanted complications, ophthalmic plaque brachytherapy was developed, based primarily on previous experience in the management of choroidal melanoma [79–81]. Various radioisotopes, including $^{103}$Pd (γ emitter) and $^{90}$Sr (β emitter), have been used. Finger et al [54] first evaluated $^{103}$Pd in 1996 with 2 prospective phase I clinical trials, the first of which treated at a retinal dose rate of 35 to 56 cGy/h for a treatment duration of 18 to 48 hours, with maximum doses to the overlying retina ranging from 12.5 to 23.62 Gy prescribed at 2-mm depth. At a mean follow-up of 19 months, 70% of patients had stable or improved VA [82]. The second phase I clinical trial treated 31 eyes (30 patients) to a mean dose of 17.62 Gy with a $^{103}$Pd source. Visual acuity at mean follow-up of 33 months was stabilized in 45% of patients, and FA demonstrated regression or stabilization of CNV in 69% [83].

Jaakkola et al [84] used $^{90}$Sr brachytherapy plaques in 20 patients (with 12 additional untreated control patients) treated with 32.4 Gy. Visual acuity at 12 months was stable or improved in 45% of treated patients and only 25% of controls. Choroidal neovascular membrane was partially or totally occluded in 74% of those treated, whereas only 25% of controls remained CNV-progression free [84]. The follow-up study of 86 participants (88 eyes), treated either with 32.4 Gy or 12.6 Gy at a depth of 1.75 mm, showed that 20% of treated patients and 42% of controls experienced visual loss ($P = .031$) at 6 months. At 36 months the benefit was no longer favorable, with visual loss present in 80% of treated patients and 84% of controls [85].

Advances in brachytherapy delivery led to the development of epimacular brachytherapy (EMB), in which radiation is delivered via a pars plana vitrectomy that allows placement of the $^{90}$Sr source at the fovea [86]. In 1 study, 50% and 76% of patients treated with 24 (n = 26) or 15 (n = 8) Gy, respectively, experienced stable or improved VA at 12 months [87].

The combination of brachytherapy and anti-VEGF therapy was tested in 34 patients treated with 24 Gy and 2 injections of bevacizumab (first injection just before or on the day of the brachytherapy procedure and the second injection 1 month post procedure). At 12-month follow-up, stable or improved vision was observed in 68%, with 38% gaining >3 lines. Cataracts occurred in 42% of eyes with phakic intraocular lens [86]. At 36-month follow-up, 10% lost >15 letters and 21% gained ≥15 letters, a result dramatically superior to those reported in most monotherapy series [88]. The MERITAGE trial treated CNV in nAMD patients (n = 53) requiring persistent anti-VEGF therapy with $^{90}$Sr (24 Gy) followed by ranibizumab injections, as needed, determined at monthly follow-up visits according to predefined criteria. At 12 months, with an average of 3.49 injections of ranibizumab after treatment, 81% of participants had stable VA, compared to only 12.4% before treatment, providing presumptive support for the hypothesis that combined therapy with the addition of radiation, specifically for those already receiving anti-VEGF therapy, might be superior for visual preservation [89]. At 24 months, with a mean of 8.7 ranibizumab treatments, fewer than one third of patients (31.9 %) had lost >15 letters [90]. Conjunctival hemorrhage (71.7%), a self-limited and not vision-threatening finding, and cataract (30.2%), easily treatable, were the most common adverse events.

After these encouraging results, 2 prospective randomized clinical trials were performed, 1 for treatment-naive individuals (the CNV Secondary AMD Treated with Beta Radiation Epiretinal Therapy [CABERNET] trial) and 1 for patients previously treated with anti-VEGF therapy (Macular Epiretinal Brachytherapy versus Lucentis-Only Treatment [MERLOT] trial). Both studies used a novel EMB system in which a probe was inserted into the posterior segment after vitrectomy to deliver $^{90}$Sr brachytherapy directly over the CNV.

The CABERNET trial randomly assigned 494 patients to $^{90}$Sr brachytherapy (24 Gy) and monthly intravitreal injections of ranibizumab (0.5 mg) for 2 months (experimental group) or monthly ranibizumab (0.5 mg) loading injections for 3 months, followed by quarterly injections (control group). The protocol was designed to demonstrate the noninferiority of the control arm at 24 months, with a 10% noninferiority margin, an endpoint that was not achieved, therefore ruling out substantial superiority.
of the experimental arm [91]. Possible explanations for failure to demonstrate efficacy in the experimental arm of the CABERNET trial include vertical dose instability with EMB during the 3 to 5 minutes of administration, a phenomenon that could result in significant underdosing of the target; the use of only treatment-naïve patients, who might have a longer time to visual deterioration, thereby reducing the statistically measurable event rate for the study; and possible altered pharmacokinetics of ranibizumab after the pars plana vitrectomy [92].

The MERLOT trial enrolled 363 patients, with final data collection for primary outcomes analysis completed in January 2015. Patients were randomly assigned to receive a single dose of 24 Gy ⁹⁰Sr, using the same device as that in the CABERNET trial, followed by ranibizumab (0.5 mg) monthly as needed versus ranibizumab (0.5 mg) monthly as needed per retreatment criteria. Results are not yet available.

SalutarisMD (Salutaris Medical Devices, Inc, Tucson, Arizona) is a new device that uses a minimally invasive retrobulbar episcleral brachytherapy application aimed at treating the nAMD. This requires surgical placement. A prospective phase I industry-sponsored clinical trial has finished recruiting patients, and results are pending.

Stereotactic Radiation Therapy

The advantage of stereotactic radiation therapy over hypofractionated EBRT lies in the ability to conform dose to the target volume while minimizing dose to surrounding normal tissue [93]. A pilot study of 94 patients [94], using dose escalation ranging from 20 to 40 Gy in 2-Gy fractions, demonstrated VA within ±3 lines with no dose dependence at 12 months. Choroidal neovascular membrane size progressed at all dose levels, and no statistically significant difference based on higher dose was observed. Vitreous hemorrhage occurred in 1 patient receiving 20 Gy. At 10-year follow-up 49% of patients had developed central geographic atrophy, and mean VA was 20/300 (compared with a baseline mean of 20/120) [95]. Complications included radiation retinopathy, confirmed in 15% of patients and suspected in 18%, with a mean onset at 5.4 years after treatment. Radiation retinopathy manifested as neovascular glaucoma in 2 patients and macular ischemia in another 2.

The IRay system (Oraya Therapeutics, Inc, Newark, California) is a stereotactic robotic radiation therapy platform designed to deliver focused, low-energy photon radiation to the central macula through the pars plana, thereby avoiding the crystalline lens. Radiation is delivered noninvasively by using 3 circular fields. Canton et al [96, 97] performed 2 prospective phase I nonrandomized, uncontrolled clinical trials, using 16- and 24-Gy stereotactic radiation therapy. In both studies, patients received ranibizumab 1 month before and 1 month after stereotactic radiation therapy, then as needed. Visual acuity was measured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, developed by the National Eye Institute to standardize testing by using the same number of letters per row with equal spacing of rows and letters on a log scale. This approach helps to eliminate inaccuracies seen in other testing methods. Six-month results in the 16-Gy group (n = 26) showed that most (96%) had lost <15 ETDRS letters of vision (an excellent outcome) and 50% had actually gained ≥15 ETDRS letters. An average of 0.5 injection of ranibizumab per patient was given in the 6 months after radiation. Toxicity included self-limited superficial punctate keratopathy in 3.85% of subjects [96]. Six-month results from the 24-Gy group (n = 19) were similar, with 100% losing <15, 79% gaining ≥0 (stabilized or improved VA), and 16% gaining ≥15 ETDRS letters, with an average of 0.4 additional injections 6 months after treatment. No adverse reactions were noted at 6 months [97]. Encouraging 12-month data for this cohort showed that all lost <15 letters, and 76% and 79% gained ≥0 letters (stable/improved VA) in the 16- (n = 28) and 24-Gy (n = 19) groups, respectively [98], suggesting the 16-Gy outcomes were equivalent to 24-Gy outcomes with less dose. A mean of 1.0 additional ranibizumab injection was given during a 12-month period with no radiation retinopathy, optic neuropathy, or cataracts.

Moshfeghi et al [99] used a “radiation first” approach and gave 16 Gy in 1 fraction followed by as-needed ranibizumab (n = 13). Eighty-five percent of participants lost <15, 54% gained ≥0, and 0% gained ≥15 ETDRS letters at 12 months. These promising results were translated into a phase III, randomized, double-masked, sham-controlled, multicenter, clinical trial (IRay Plus Anti-VEGF Treatment for Patients with Wet AMD [INTREPID] trial) [100–102], with a primary outcome of number of as-needed 0.5-mg ranibizumab injections and secondary outcomes of ETDRS VA and CNV size. Inclusion in the study (n = 230) required detection of CNV within 3 years, ≥3 injections of an anti-VEGF agent in the past year, and an ongoing need for additional anti-VEGF therapy. Patients were randomly assigned to 16- (n = 75), 24- (n = 75), or 0-Gy (sham) radiation therapy (n = 80), with a baseline injection of ranibizumab followed by as-needed ranibizumab according to predefined treatment criteria. At 2 years, patients receiving 16 and 24 Gy had a statistically significant decrease in ranibizumab injections with a mean of 4.5 (P = .008) and 5.4 (P = .09) ranibizumab injections, respectively, compared to a mean of 6.6 ranibizumab injections for sham radiation [102]. Although mean VA was stable in both treatment groups at 12 months, VA gains seen in the early weeks of the study returned to or near baseline over the same period [100]. Results were as follows at 24 months in the
16-Gy, 24-Gy, and sham groups: 68%, 75%, and 79% lost < 15 ETDRS letters; 32%, 43%, and 38% gained ≥ 0 ETDRS letters; and 3%, 1%, and 3% gained ≥ 15 ETDRS letters. Mean CNV size was estimated to decrease by 0.1 mm² in all groups. Although VA and CNV size results did not differ significantly in the treated and control groups, the study was not designed to demonstrate superiority or noninferiority.

Overall, the stereotactic radiation therapy outcomes to date demonstrate stabilization of VA with reduced need for anti-VEGF treatment. These results could decrease financial and social burden to the patient by reducing the number of intravitreal injections and clinic visits as well as by reducing complications from repeated intravitreal injections, including endophthalmitis, ocular hypertension, geographic atrophy, and arteriothrombotic events. Anticipated 3-year safety analysis data will help guide future recommendations regarding combination therapy using stereotactic radiation therapy and anti-VEGF agents.

Proton Therapy

Yonemoto et al [103] published their proton therapy experience with 21 patients with CNV treated with 7.27 Gy in 1 fraction (100 Mev protons) between March and August 1994. Fifty-three percent of patients showed regression or stabilization with FA. At a mean follow-up of 11.6 months, visual acuity showed that 58% of patients had improved or had stable vision. Another phase I/II dose-escalation study enrolled 27 patients between September 1994 and January 1996. These patients were treated with a single 12.73 Gy fraction using 100-MeV protons, and they were compared with patients who received 7.27 Gy in 1 fraction [104]. Actuarial lesion control at 21 months was 36% for patients who received 7.27 Gy and 89% for patients who received 12.73 Gy. Of patients with stable lesions, 77% achieved improved/stable VA, compared with 44% of patients with active lesions. The actuarial mean visual loss of proton-treated patients was 0% at 24 months. Increased morbidity (not vision limiting) was associated with higher dose (0% for 7.27 Gy and 26% for 12.73 Gy), which is likely a consequence of giving this total dose in 1 fraction. Flaxel et al [105] reported a mean 22.1-month follow-up for this same cohort. Twelve-month VA was stable in 44% and 75% of patients receiving 7.27 and 12.73 Gy, respectively. Fluorescein angiography showed greater and more continued regression of nAMD at the higher dose. Between October 1995 and February 2000, a total of 166 patients from Harvard (Cambridge, Massachusetts) were randomly assigned to 14.55 and 21.82 Gy proton therapy. Twelve months after completion of treatment, 42% and 35% lost ≥ 3 lines of vision from baseline. At 24 months, loss of ≥ 3 lines of vision increased to 62% and 53% in the 14.55-Gy and 21.82-Gy groups, respectively (P = .40) [106]. No significant difference was found in radiation complications between the 2 groups (15.7% and 14.8% for 14.55 and 21.82 Gy, respectively). Ciulla et al [107] treated 37 patients with 14.55 Gy protons in 2 fractions and compared results with those from sham treatments. They observed a nonstatistically significant trend toward stabilization of VA. Accurral was halted because of ethical concerns over those assigned to sham treatment given the anticipated near-term FDA approval of verteporfin. A study from Nice, France, used 9.09 Gy in 58 patients [108]. At 18-month follow-up, VA was stable in 61%, and FA showed stable CNV in 66.6%. Three patients had progressive CNV, and 4 had submacular hemorrhage. A recent pilot study with 3-year follow-up [109] found that ranibizumab administered at 4 monthly injections and combined with 21.82 Gy (in 2 fractions, 24 hours apart) of proton beam radiation for nAMD in 6 patients (4 of whom were treatment-naïve) demonstrated no complications of treatment; furthermore, 3 of the 4 treatment-naïve patients required no further treatment. These early findings lend additional credence to radiation therapy as a useful adjunct to antiangiogenic agents.

The ongoing Prospective Randomized Trial of Proton Beam Combined with Anti-VEGF Therapy for Exudative AMD (PBAMD2 trial) is expected to finish accrual in December 2016. The trial randomly assigns patients to 21.82 Gy proton therapy plus anti-VEGF, 14.55 Gy proton therapy plus anti-VEGF, or sham irradiation plus anti-VEGF.

Stem Cell Transplant in AMD

Stem cell therapy is in its infancy for nAMD and many challenges exist regarding safety and prevention of rejection of transplanted stem cells. Examples of ongoing trials in dry AMD are using bone marrow CD34+ stem cells (NCT01736059 and NCT01920867), human embryonic stem cells (hESCs) (NCT01344993), and human CNS stem cells (NCT01632527). These cells differentiate into RPE and are surgically placed subretinally to replace the damaged RPE. An open-label phase I/II trial (NCT01344993) using hESCs for dry AMD showed that at 12 months (in eyes that did not develop cataract or require ocular surgery during follow-up) VA increased by 8 ETDRS letters (range, 4–23) for dose group 1 (50 000 cells; n = 3), 8 ETDRS letters (range, 2–14) for dose group 2 (100 000 cells; n = 2), and 15 ETDRS letters (range, 13–44) for dose group 3 (150 000 cells; n = 3), and this was statistically significant (P = .0117) [110]. The first nAMD stem cell trial is a phase I trial from Japan at the research institution RIKEN. RIKEN is using human-induced pluripotent stem cells (hiPSCs), which have been shown to
differentiate into hiPSC-RPE and are used as a graft for tissue replacement therapy in AMD [111]. Results from these trials are pending and accrual is ongoing.

Discussion

The societal burden of AMD cannot be overstated, and this devastating disease will continue to have a significant impact worldwide, especially in developed countries. Current standard therapy is anti-VEGF treatment. Antiangiogenic therapy has proven effective for some patients, with 40% of individuals experiencing improvement in vision at 12 months, whereas 60% continue to have progressive decline in vision [20, 22]. Antiangiogenic injections, although well tolerated, are costly, necessitate repeated office visits, and carry the risk of endophthalmitis [20, 22]. A cost-of-treatment review of Medicare Part B for bevacizumab and ranibizumab found that 218 000 people were treated with bevacizumab (off-label) and ranibizumab (FDA approved) in 2009 [112]. Estimated reimbursement for covered drugs furnished incident to physician services totaled $40 million for 936 382 bevacizumab treatments and $1.1 billion for 696 927 ranibizumab treatments. Moja et al [113] showed bevacizumab and ranibizumab to be equivalent in numbers of serious systemic adverse events in the first 2 years of treatment, except for gastrointestinal disorders. Therefore, bevacizumab, although off-label, may be the more appropriate choice for treatment of nAMD from a cost perspective [112]. This also makes a strong case for combination therapy that would decrease the frequency of injections while maintaining or improving vision.

Rationale for Combining Antiangiogenic Agents with Radiation Therapy

Unlike anti-VEGF agents, radiation affects both the vascular and avascular fibrous components of nAMD. Radiation can be antiangiogenic, anti-inflammatory, and antifibrotic [114]. Although radiation retinopathy is a potential adverse effect of radiation, multiple studies have shown that bevacizumab is beneficial in treating this condition [115–118]. The ongoing Treatment of Radiation Retinopathy trial has yet to accrue a sufficient patient number to study ranibizumab or triamcinolone acetonide versus observation in prevention of radiation retinopathy following irradiation for choroidal melanoma [119].

Previous trials in human umbilical vein endothelial cells and radiation-resistant p53-dysfunctional tumor xenografts derived from SW480 colon adenocarcinoma cells that received combination novel anti-VEGF (PTK787/ZK222584) and ionizing radiation (5 or 10 Gy) demonstrated promising results. Even in the absence of anti-VEGF therapy, radiation-induced arrest of cell proliferation and combined antiangiogenic and radiation therapy showed additive antiproliferative effect without supra-additive cytotoxic effects [120].

Case for Proton Therapy over Photon Therapy

The previously mentioned modalities and devices for photon radiation delivery have several disadvantages. NeoVista (Newark, CA) and Salutaris require surgery; one is actually an intraocular approach and the other requires mobilization of the globe to reach the posterior portion to place the radioactive probe over the lesion. In both cases, because the radioactive probes have a finite size, the CNV has a varying size, and of the difficulty in determining the confines, the lesions could be overtreated or undertreated, and technical challenges in positioning could lead to “geographic” misses. Moreover, surgery in this patient group is associated not only with discomfort but also with significant complications.

Using external-beam photon therapy, x-rays are directed at a target from outside the eye. Unlike photons, protons have the potential to deliver a focal dose to the target while minimizing radiation to adjacent normal tissues. With photons, radiation is delivered not only to the posterior retina but also to the bilateral orbits, contralateral eye, and surrounding soft tissues. The proton beam can be configured to allow no radiation to the contralateral orbit, little if any to the soft tissues, and a minimal dose to the normal retina. In addition, proton treatment planning software allows importing of the FA-identified CNV into the eye model to verify location in relation to other ocular structures. This allows for a customized proton radiation portal and an appropriate gaze for delivery of optimum treatment. Additionally, this allows for targeting the therapy based on irregular shape and thickness—which cannot be achieved as precisely and effectively with photon therapy. A high dose rate is needed to limit the amount of time a patient is required to maintain eccentric gaze during delivery of a large fractional dose. This can be accomplished by using a proton eyeline, which ensures a high dose rate (>30 Gy/min) while avoiding critical structures by using sharp dose gradients and limiting patient gazing time. The patient is positioned in the line of a fixed proton beam. Before starting the treatment, the patient’s head is immobilized and position of the eye is set. Treatment then begins after confirmation of adequate positioning and head fixation. Using this therapy is preferred over treatments with proton therapy not designed to deliver stereotactic radiation [121].

Rice et al. (2016), Int J Particle Ther
Case for Proton Therapy with Anti-VEGF for nAMD

We expect that the increasing availability of proton treatment in the United States will result in more studies for nAMD. Given the current need, further investigation should focus on proton beam radiation in tandem with antiangiogenic therapy. Findings to date suggest that protons could have a role as an effective noninvasive treatment for nAMD.

Given preliminary evidence supporting the use of stereotactic radiation therapy [100–102] and proton therapy [109], it is reasonable to consider a randomized, double-masked, prospective phase III clinical trial to determine which combination of therapeutic modalities has the best outcomes and safety profiles. A potential trial design might be 3 armed and include the following: (1) stereotactic radiation therapy given with a dedicated stereotactic radiation delivery system combined with antiangiogenic therapy; (2) proton therapy delivered via a dedicated proton eyeline combined with antiangiogenic therapy; and (3) antiangiogenic therapy alone. Such a study could provide valuable data to support clinical implementation of proton therapy as an adjunct approach in this difficult and debilitating disease setting.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: MPM has served as a consultant for Cavion, Novocure, and Novartis; has clinical trial research funding from Cellectar and Novocure; and previously served on the Board of Directors of Pharmacyclics. SRR and MSJK have no conflicts of interest to disclose.

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