Anti-VEGF Therapy Shows Benefit in the Treatment of Radiation Maculopathy

Evidence is mounting for the efficacy of this approach.

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Mounting evidence suggests that anti-VEGF agents are efficacious in the treatment of radiation maculopathy. Although no prospective, randomized trials have been conducted to support the use of these agents, a survey of 15 leading ocular oncologists found that 13 (87%) routinely use anti-VEGF agents to treat radiation maculopathy.[1]

Although experience suggests that anti-VEGF agents work in the treatment of radiation maculopathy and retinopathy, many questions and controversies remain, including (1) when to start treatment; (2) how frequently to treat; (3) which anti-VEGF agent to use; (4) whether and when to use combination treatment with corticosteroids, laser photocoagulation, or focal laser; and (5) when, if ever, to stop treatment. In publications to date, these parameters vary considerably in each case series.

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BACKGROUND

As a result of the Collaborative Ocular Melanoma Study (COMS), treatment of uveal melanoma consists primarily of globe-salvaging therapy with plaque brachytherapy. However, despite globe-salvaging treatment, after 2 to 3 years radiation retinopathy limits visual acuity in most cases. The COMS investigators found that median visual acuity at year 3 was 20/125, with 43% of patients achieving 20/200 visual acuity or worse and 49% losing 6 or more lines of vision.[2] Shields et al reported on more than 1100 patients treated with plaque brachytherapy for uveal melanoma.[3] At 5 years, 34% of these patients had visual acuity of 20/200 or worse, and this percentage jumped to 68% at 10 years.

On quality-of-life questionnaires, patients treated with plaque brachytherapy reported better function in driving and peripheral vision up to year 2 than patients undergoing enucleation. However, from years 3 to 5, there was no difference in these parameters regardless of treatment.[4]

Visual acuity decline can be attributed to radiation retinopathy and radiation maculopathy. Risk factors for these radiation-related complications include radiation dose, treatment proximity to the fovea, tumor size, tumor-associated retinal detachment, and history of diabetes.[2]

These studies illustrate that, despite globe-salvaging treatment, most patients are legally blind in the treated eye, resulting in a profound effect on their quality of life.

Spectral-domain optical coherence tomography (SD-OCT) in patients after brachytherapy shows that macular edema is 1 of the first signs of radiation maculopathy.[5] To date, no treatment for radiation maculopathy or radiation retinopathy has been approved by the US Food and Drug Administration. However, the off-label use of intravitreal anti-VEGF agents has shown significant promise in stabilizing and often improving visual acuity in patients with radiation maculopathy and macular edema following plaque brachytherapy for uveal melanoma.

WHEN TO INITIATE TREATMENT

A fundamental question in the management of radiation maculopathy and retinopathy is when to start treating with anti-VEGF agents. Eyes with radiation maculopathy, also called radiation-induced macular edema, are at risk for severe visual loss.[6] As a result, some experts advocate treating at the first sign of radiation-related vascular changes or macular edema.

SD-OCT is an integral component of post-brachytherapy follow up to detect the earliest signs of macular edema. There is evidence that radiation maculopathy as seen on SD-OCT occurs at a mean of 12 months, but some patients can have edema as early as 4 months after plaque therapy.[6]

Following plaque brachytherapy for uveal melanoma, aqueous levels of VEGF-A are significantly higher than in normal controls.[7] Early radiation maculopathy may occur secondary to a toxic tumor effect or from tumor ischemia following treatment. Delayed radiation maculopathy likely results from radiation-related effects on the retinal vasculature, causing vascular permeability and macular edema.

Several studies have demonstrated the efficacy of anti-VEGF agents against radiation maculopathy when instituted at the first signs of macular edema on OCT. Initial studies by Mason et al showed that a single intravitreal bevacizumab (Avastin, Genentech) injection resulted in improved visual acuity and edema on OCT at 6 weeks compared with baseline.[8] However, macular edema recurred with resultant worsening of vision at 4 months. The experience with these few patients demonstrated that a single treatment has a transient effect, and long-term treatment with repeated injections is needed. A larger, retrospective study subsequently showed that 51% of patients treated with intravitreal bevacizumab maintained 20/50 or better vision at a median of 36 months after plaque brachytherapy.[9] Patients who maintained better vision had better visual acuity at the initiation of anti-VEGF therapy. This study suggests the importance of early identification and treatment of patients with radiation maculopathy to stabilize and potentially improve vision.

An alternative treatment strategy is the use of intravitreal anti-VEGF agents immediately following plaque removal and at regular postoperative intervals. This treatment regimen aims to prevent radiation maculopathy in hopes of maintaining and preserving visual acuity. Shields et al reported on a series of 292 patients treated with intravitreal bevacizumab immediately following plaque removal, and then every 4 months for 2 years, compared with control patients who did not receive anti-VEGF treatment.[10] OCT-evident macular edema at 2 years was seen in 26% of the treated group compared with 40% of control patients. Patients treated with intravitreal bevacizumab were less likely than control patients to lose 3 or more lines of vision (33% vs 57%, respectively) and to have vision of 5/200 or worse (15% vs 28%, respectively). Additionally, combined brachytherapy with immediate intravitreal bevacizumab led to enhanced resolution of tumor-related exudative detachment and accelerated tumor volume reduction.[11]

Kim et al reported on the adjuvant use of intravitreal ranibizumab (Lucentis, Genentech) with proton beam irradiation for the treatment of uveal melanoma.[12] Patients were treated at the time of irradiation and every 2 months thereafter. At 12 months, visual acuity was 20/200 or better in 67% of patients with large tumors (> 15 mm basal diameter, > 5 mm height) and 100% of those with small tumors (< 15 mm basal diameter, < 5 mm height). At 24 months, visual acuity was 20/200 or better in 86% of patients with large tumors and 100% of those with small tumors. Additionally, 89% of patients with small tumors had 20/40 or better vision at 24 months.

HOW FREQUENTLY TO TREAT

The literature reporting the use of anti-VEGF therapy for neovascular age-related macular degeneration (AMD), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and diabetic macular edema (DME) describes 3 principal treatment regimens: (1) fixed interval; (2) as-needed or PRN treatment based on OCT and/or visual acuity; and (3) treat-and-extend, with extension of intervals between injections.

Most studies of anti-VEGF treatment for radiation maculopathy have used fixed-interval dosing, ranging from every month to every 4 months. These treatment frequencies often overlap with the frequency with which patients are followed after plaque brachytherapy. However, as this disease appears to be VEGF-related, one may ask, "Why not treat radiation maculopathy with a regimen similar to those used for other retinal diseases

driven by VEGF involvement?"

Neovascular AMD and retinal vascular diseases are often treated monthly until the macula is dry or until the patient shows significant improvement in disease activity, based on SD-OCT and corresponding improvement in visual acuity. After consolidation with initial monthly therapy, patients are either followed with SD-OCT and treated PRN based on disease activity and/or vision, or with a treat-and-extend strategy.

Mashayekhi et al reported short-term follow-up of 36 patients treated with monthly intravitreal bevacizumab for radiation maculopathy.[13] At 4 to 6 months, 86% of patients had stable vision and 42% had improved visual acuity. Central macular thickness (CMT) on SD-OCT improved in 56% of patients. This study demonstrated that aggressive treatment of radiation maculopathy can result in stabilized and often improved vision.

While these short-term results were favorable, results of longer-term studies are needed. Evidence is mounting that anti-VEGF treatment can preserve visual acuity in many patients who may otherwise have progressed to moderate or severe vision loss. Further studies are needed to determine the most effective treatment interval. However, head-to-head comparisons in a randomized, controlled trial are likely not feasible.

WHICH ANTI-VEGF AGENT TO USE

In the current era of pharmacologic retina, several anti-VEGF medications are available to treat patients with radiation maculopathy. VEGF has been shown to be elevated in eyes following plaque brachytherapy for uveal melanoma. Bevacizumab and ranibizumab are commonly used to treat retinal vascular diseases. Ranibizumab has been shown to be efficacious in stabilizing and often improving visual acuity in CRVO and BRVO.[14,15] Aflibercept (Eylea, Regeneron) has demonstrated similar efficacies.[16-19] Intravitreal bevacizumab is most commonly used as an off-label treatment for radiation maculopathy. There are few if any reports in the literature regarding treatment with other agents.

Aflibercept is inherently different than ranibizumab and bevacizumab, in that it is a decoy receptor fusion protein composed of VEGF receptors 1 and 2 (VEGFR-1 and VEGFR-2). This molecule binds all isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF).[16,17] Aflibercept has a higher binding affinity and the potential for longer intervals between injections. Prospective studies investigating the use of different anti-VEGF agents in the treatment of radiation maculopathy are anticipated. Until their results become available, intravitreal bevacizumab will likely remain the treatment of choice for radiation maculopathy.

BENEFIT OF COMBINATION TREATMENT?

Combination treatments are often employed in other retinal vascular diseases such as diabetic retinopathy, DME, BRVO, and CRVO. In combination with anti-VEGF agents, frequently used adjuncts include corticosteroids (eg, triamcinolone, dexamethasone) and laser application (panretinal photocoagulation, sectoral panretinal photocoagulation, focal laser).

Corticosteroids have been shown to be effective as a sub-Tenon injection following plaque brachytherapy and at 4-month intervals thereafter.[20] The incidence of radiation maculopathy was 36% in the treatment group and 58% in the control group. Additionally, moderate to severe vision loss were seen less frequently in the treatment group (moderate 31%; severe 5%) compared with the control group (48% and 15%, respectively). Shah et al investigated the use of intravitreal triamcinolone in combination with anti-VEGF treatment in 25 patients with severe radiation maculopathy.[21] Consolidation treatment with intravitreal corticosteroids stabilized visual acuity and macular edema in this subset of patients with severe radiation maculopathy. In addition, 36% of patients were able to maintain 20/50 or better vision. Mieler et al reported a significant reduction in macular edema on SD-OCT with a combination of triamcinolone and bevacizumab compared with monotherapy.[22] However, in their report, visual acuity did not differ between combination and monotherapy.

As in the studies noted here, patients receiving combination treatment often have persistent disease that does not respond to anti-VEGF therapy alone. These patients often have chronic ellipsoid zone loss and, despite anatomic improvement, visual acuity may be limited.

Laser photocoagulation was used to treat radiation retinopathy before the advent of anti-VEGF agents.[23] In an intriguing paper, Finger et al described the use of sectoral laser photocoagulation to the tumor and margins of 2 to 3 mm following plaque brachytherapy.[24] In this study, 45 patients with radiation retinopathy were treated at the first signs of disease. Retinopathy regression was seen in 64% of patients, but visual acuity loss of 3 or more lines was seen in 47% of patients. Among those who lost vision, radiation maculopathy was the cause in a third of cases. Interestingly, 16 patients designated as "high risk" were treated with prophylactic laser, and only 18% developed radiation-related changes, all of which regressed with further laser treatment. Additionally, no patients in the prophylactic laser group lost 3 or more lines of vision.

Treatment with corticosteroids or laser photocoagulation may provide additional benefits when used

in combination with anti-VEGF therapy. These areas represent avenues for further research.

WHEN TO STOP TREATMENT

Patients receiving intravitreal anti-VEGF agents frequently ask when they can stop treatment. The answer is not clear, and it is often individualized. As with other retinal vascular diseases and neovascular AMD, some patients can be observed off treatment, some remain stable at longer treatment intervals, and some need frequent injections to maintain disease stabilization.

Some experts advocate stopping or reducing treatment if there is not a significant anatomic or visual response with repeated treatment. However, in patients who have demonstrated improvement in visual acuity or reduction in macular edema, treatment should be continued and monitored with serial SD-OCT and clinical examinations.

Individualized responses to anti-VEGF agents are not fully understood, but there are likely genetic and anatomic variables to consider. For radiation maculopathy, it is not known how long patients must be treated.

CONCLUSIONS

Studies to date do not provide long-term data to support answers to many questions: Is there a critical period for treatment after which the disease will stabilize? Can combination treatment with laser and anti-VEGF agents decrease the burden of frequent injections? Does treatment reduce the risk of neovascular glaucoma?

What is known is that prophylactic anti-VEGF treatment or treatment once radiation maculopathy commences can often stabilize disease, potentially prevent moderate to severe visual loss, and sometimes improve vision. The authors believe that, if the eye in question belonged to 1 of us or to a family member, we would recommend early treatment with an anti-VEGF agent in hopes of preserving as much vision as possible.

Finally, does anti-VEGF treatment benefit patients with radiation maculopathy following treatment with radiation for uveal melanoma? Although long-term, randomized, controlled clinical trials are not available, several clinical series show a benefit of anti-VEGF therapy in stabilizing and often improving visual acuity. Prior to the availability of anti-VEGF treatment, no proven therapy for radiation maculopathy existed, and we can now offer our patients treatment for an otherwise blinding disease. Questions remain regarding the optimal treatment protocol, but evidence suggests that a variety of treatment protocols have provided significant visual benefits, and these treatments should not be withheld. ■

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