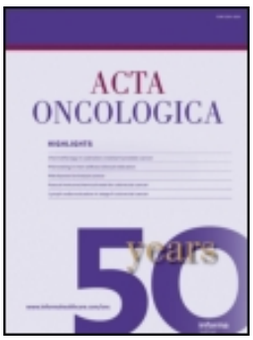

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REVIEW ARTICLE

Current treatments for radiation retinopathy

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Abstract

Background. To review the currently available therapeutic modalities for radiation retinopathy (RR), including newer investigational interventions directed towards specific aspects of the pathophysiology of this refractory complication. *Methods.* A review of the literature encompassing the pathogenesis of RR and the current therapeutic modalities available was performed. *Results*. RR is a chronic and progressive condition that results from exposure to any source of radiation. It might be secondary to radiation treatment of intraocular tumors such as choroidal melanomas, retinoblastomas, and choroidal metastasis, or from unavoidable exposure to excessive radiation from the treatment of extraocular tumors like cephalic, nasopharyngeal, orbital, and paranasal malignancies. After the results of the Collaborative Ocular Melanoma Study, most of the choroidal melanomas are being treated with plaque brachytherapy increasing by that the incidence of this radiation complication. RR has been reported to occur in as many as 60% of eyes treated with plaque radiation, with higher rates associated with larger tumors. Initially, the condition manifests as a radiation vasculopathy clinically seen as microaneurysms and telangiectases, with posterior development of retinal hard exudates and hemorrhages, macular edema, neovascularization and tractional retinal detachment. Regrettably, the management of these eyes remains limited. Photodynamic therapy, laser photocoagulation, oral pentoxyphylline and hyperbaric oxygen have been attempted as treatment modalities with inconclusive results. Intravitreal injections of anti-vascular endothelial growth factor such as bevacizumab, ranibizumab and pegaptanib sodium have been recently used, also with variable results. *Discussion*. RR is a common vision threatening complication following radiation therapy. The available therapeutic options are limited and show unsatisfactory results. Further large investigative studies are required for developing better therapeutic as well as preventive treatment strategies.

Radiation retinopathy (RR) is a chronic and progressive condition that may result from the exposure to any source of radiation including: external beam radiation, plaque brachytherapy, proton beam radiation, helium ion radiotherapy, and gamma knife radiotherapy [1–5]. RR may be secondary to the treatment of intraocular tumors such as choroidal melanomas, retinoblastomas, and choroidal metastasis or from unavoidable exposure to excessive radiation from the treatment of cephalic, nasopharyngeal, orbital, and paranasal tumors among other malignancies [2,6–8].

Following the Collaborative Ocular Melanoma Study (COMS) therapeutic options for choroidal melanomas, the most common primary malignancy of the eye, have shifted from enucleation of the eye to plaque brachytherapy for medium-size melanomas since the survival rate has been found to be similar [9,10]. This shift towards globe salvaging strategies has increased the use of radiation and consequently increased its complications with the incidence of RR ranging from 3 to over 20% [11–13]. A recent retrospective study reported an incidence of RR with associated retinal neovascularization (proliferative RR) of 5.8% at five years and 7% at ten and 15 years in 3 841 eyes treated with plaque radiotherapy for uveal melanoma [6].

The development of RR has always been related to the total dose of radiation administered to the retina, accepting 35 Gy as the upper limit of safe total dosage [14,15]. Although cases of radiation retinopathy have been reported after much lower levels of irradiation [16,17]. Several studies involving the use of hyperfractionated radiotherapy and reducing the

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radiation given by plaque brachytherapy from 85 Gy, as indicated by the COMS to a range of 56–69 Gy were shown to have the same survival and local tumor control [18,19]. On the other hand, several studies have found various risk factors for developing RR, such as shorter tumor distance from the optic nerve, preexistent diabetes mellitus, and young age, unrelated to the amount of radiation given [12,20].

Pathogenesis

Retinal vascular endothelial cell damage is believed to initiate the development of RR [21]. The structure of the heterochromatic nuclear DNA of endothelial cells permits less enzymatic repair, rendering dividing retinal vascular cells more susceptible to ionizing radiation [22]. In addition, a small percentage of non-mitotic cells will suffer immediate death if enough radiation is absorbed during the initial insult. Cell death stimulates division and migration of cells in the vicinity to repair the discontinuity in the vessel wall. Migratory cells may also succumb to the effects of radiation during mitosis leading to a vicious cycle that might trigger the clotting cascade due to incompetence of the vascular endothelium leading to clinically observable retinopathy in the form of microaneurysms, telangiectases, neovascularization, vitreous hemorrhage, macular edema and tractional retinal detachment [23–25] (Figure 1). From a clinical standpoint, RR can be classified as non-proliferative and proliferative, both of which may be associated with macular edema that has been associated with a worse visual prognosis [26].

Management

The management of RR remains to be challenging. The following discussion will address currently available therapeutic options including newer, investigational interventions directed towards specific aspects of the pathophysiology of this refractory complication.

Retinal laser photocoagulation

Light Amplification by the Stimulated Emission of Radiation (LASER) can produce thermal denaturation of tissue when a high intensity laser source of appropriate wavelength is absorbed by hemoglobin and other ocular tissues [27,28]. There is a broad spectrum of indications for laser photocoagulation in ocular diseases such as diabetic retinopathy, branch retinal vein occlusions, and treatment of retinal tears [29–32]. Photocoagulation may also be employed as a prophylaxis against neovascular glaucoma and to treat macular edema secondary to RR [33–36] (Figure 2).

As for RR, several studies have explored the effectiveness of this treatment modality. Finger et al. investigated the use of sector argon laser photocoagulation in early stages of RR (mean laser sessions of 2.75) where they observed regression of RR in 64% of the eyes that had developed RR and found that 18.75% of the "high risk" patients who were treated prophylactically developed RR [36].

Laser photocoagulation has been used for the treatment of macular edema secondary to RR. Hykin et al. found that 42% of the affected eyes experienced at least an improvement of one line on the Snellen

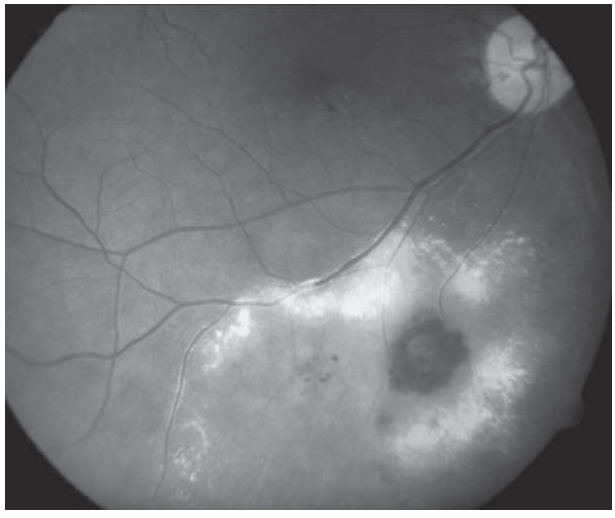

Figure 1. Fundus photograph of a right eye showing proliferative and exudative radiation retinopathy following brachytherapy with ^{106}Ru for a choroidal melanoma. Note the vascular microaneurysm, intraretinal hemorrhage, and exudation from new and incompetent blood vessels.

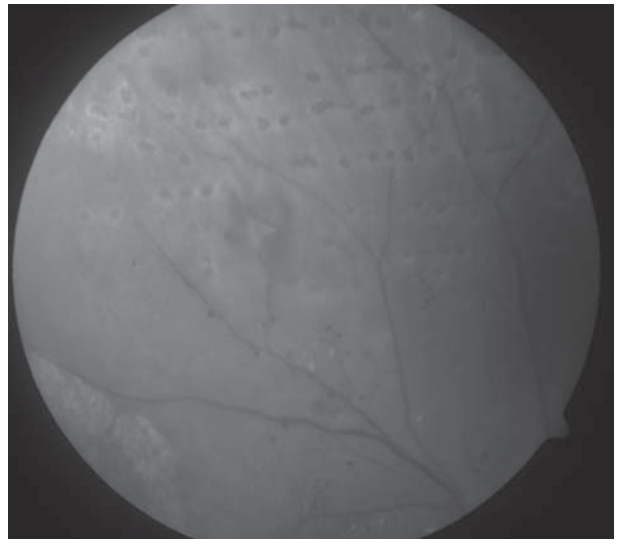

Figure 2. Fundus photograph of the right eye of a patient treated with ^{125}I plaque for a choroidal melanoma showing microaneurysms, telangiectases, and retinal neovascularization secondary to radiation retinopathy. Note the laser photocoagulation scars.

chart at six months when compared to the observational group; however the difference at 12 and 24 months was not significant [37]. In the same token, Kinyoun et al. observed an improvement in the visual acuity in 67% of the eyes after an average of one retreatment for recurrent macular edema, concluding that this treatment modality might be more effective in preventing further visual deterioration rather than restoring vision [34,35]. In addition to that, panretinal photocoagulation was found to be effective in the treatment of the retinopathy following radiation for head and neck tumors [38].

Retinal photocoagulation remains the gold standard in the treatment of most forms of ischemic retinopathies; however the beneficial effect for prophylactic photocoagulation in RR remains unjustified in the absence of larger randomized, controlled studies especially that not all patients treated with radiation will develop RR. This raises the question if it is justified to ablate the retina surrounding the tumor prophylactically.

Photodynamic therapy

Photodynamic therapy (PDT) is a two step process in which an intravenous infusion of verteporfin is followed (typically 15 minutes later) by irradiance with a 689 nm laser for about 83 seconds. Verteporfin binds to low density lipoproteins in the plasma during this process, which are then preferentially bound by choroidal neovascular membranes (a neovascular network of new blood vessels in the choroid). Application of laser energy results in formation of toxic oxygen species that induce thrombosis of choroidal neovessels [39,40]. PDT was approved by the United States Food and Drug Administration (US FDA) in 2000 for the treatment of predominantly classic subfoveal lesions associated with age-related macular degeneration.

A small study showed the effect of PDT in four patients with RR related macular edema. All eyes demonstrated improvement in visual acuity [41]. A case study by Lee et al. reported visual improvement six months after PDT in a patient with choroidal neovascular membrane secondary to external beam radiation [42].

The use of PDT in RR has been insufficiently investigated so far, with the few studies done showing a beneficial effect; however, more robust evidence is required.

Corticosteroids

Inflammation is implicated in the pathogenesis of an increasing number of ocular diseases. Corticosteroids are frequently employed in order to inhibit migration and activation of inflammatory cells. Corticosteroids block the pathways of selectins, integrins, Inter-Cellular Adhesion Molecule 1 (ICAM-1), tumor necrosis factor-α and monocyte chemo-attractive protein-1 (MCP-1) at various levels [43]. Corticosteroids also have a direct angiostatic effect by up-regulating the extracellular-matrix protein plasminogen activator inhibitor, and reducing vascular permeability [43]. These characteristics may provide a greater benefit than therapeutic modalities that block a single molecule or pathway.

Since the early 1980s, intravitreal triamcinolone acetonide has been used to treat vitreo-retinal proliferation [44]. In preclinical studies triamcinolone inhibited cytokine-induced upregulation of ICAM-1 by endothelial cells and reduced hypoxia-induced upregulation of VEGF by cultured retinal pigment epithelium cells [45]. As for its use for RR treatment, Shields et al. reported the effect of intravitreal triamcinolone (4 mg/1 mL) in a prospective, nonrandomized, single-center case series of 31 patients with visually symptomatic radiation-induced macular edema after plaque radiotherapy. They reported that after intravitreal injection of triamcinolone acetonide, visual acuity was stable or improved in 91% of patients by one month and 45% by six months. There was also a decrease in the mean central subfield foveal thickness measured by optical coherence tomography (OCT) [46]. Suttler et al. also reported the benefit of triamcinolone use in a patient who developed RR six years after external beam irradiation (5 400 rad [54 Gy] in 30 fractions [5 fractions per week]) for a left parotid gland carcinoma [47].

Despite the potential benefits, intravitreal injection of triamcinolone actetate is associated with side effects, including glaucoma, cataracts, retinal detachment, and endophthalmitis [48,49]. This has lead to investigating periocular triamcinolone in an effort to avoid or reduce the incidence of these side effects.

Horgan et al. evaluated the potential benefit of periocular depot triamcinolone in the prevention of macular edema secondary to ^{125}I plaque for uveal melanoma. They found that this treatment modality significantly decreased the risk of macular edema after plaque radiotherapy, but did not significantly alter the rate of vision loss at 24 months of follow-up [50]. Recently, a larger prospective, randomized, controlled clinical trial conducted by this same group, in patients with uveal melanoma treated with ^{125}I plaque showed that periocular injection of triamcinolone (40 mg/1 mL) given at the time of the plaque application and four and eight months later effectively reduced the risk of macular edema and moderate vision loss for 18 months [51].

Anti-vascular endothelial growth factor agents (anti-VEGF)

A strong relationship has been found between vascular endothelial growth factor (VEGF) and the development of diabetic retinopathy, exudative age-related macular degeneration, and ocular ischemic diseases.

VEGF is a protein secreted under hypoxic conditions that promotes vascular leakage and angiogenesis [52]. Animal models have demonstrated the development of the pathologic changes characteristic of diabetic retinopathy following intravitreal injection of VEGF [53,54].

Bevacizumab. Bevacizumab (Avastin, Genentech) is a potent monoclonal antibody that blocks all VEGF-A isoforms. Bevacizumab was the first anti-VEGF therapy approved by the US FDA for the treatment of colorectal, breast, and lung cancer [55]. After the results of preliminary studies with a similar molecule, ranibizumab (Lucentis, Genentech) in the treatment of exudative age-related macular degeneration, ophthalmologists were motivated to use bevacizumab off-label, both systemically and intravitreally, to treat this disease as well as other forms of choroidal neovascular membranes, neovascular glaucoma and diabetic retinopathy [56–59]. Following that, the efficacy of *bevacizumab* for the treatment of RR was investigated (Figure 3).

A retrospective case series of ten consecutive patients evaluated the effect of intravitreal bevacizumab on macular edema related to RR after brachytherapy for choroidal melanoma. These patients were treated with a single intravitreal injection of bevacizumab after the development of macular edema. The mean visual acuity improved from 20/100 to 20/86 at six weeks and 20/95 at four months. Mean foveal thickness measured by OCT was 482 μm before injection, 284 μm six weeks after injection, and 449 μm four months after injection [60].

Gupta et al. evaluated the safety and efficacy of 1–2 intravitreal injections of bevacizumab in an interventional case series of five patients who developed radiation related macular edema after ^{106}Ru for choroidal melanoma. Two of the five patients showed resolution of macular edema while the other three patients who had a longstanding disease showed no improvement after a single suggesting that younger patients with shorter duration of macular edema benefited the most [61].

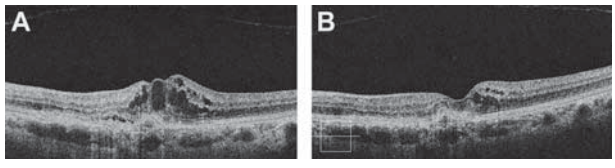

Figure 3. Optical coherence tomography image in a patient with radiation retinopathy following ^{106}Ru brachytherapy for choroidal melanoma. (A) Note the increased foveal retinal thickness with evident cystic spaces. (B) Image of the same patient taken 12 weeks after two intravitreal injections of bevacizumab. Note the significant decreased in the retinal thickness and resolution of the cystic spaces.

Finger et al. evaluated the effectiveness of intravitreal bevacizumab for radiation retinopathy in six patients who underwent plaque radiotherapy. Following periodic (every six to eight weeks) intravitreal bevacizumab (1.25 mg in 0.05 mL), there was a decrease in macular edema, improvement or maintenance of visual acuity and reduced hemorrhage and retinal edema [62]. Shortly thereafter, the same group published results of 21 patients consistent with the first one whereby reduction in retinal hemorrhage, exudation, and edema was noted after the treatment and visual acuities were stable or improved in 86% with 14% of patients regaining two or more lines of visual acuity [63]. No ocular or systemic side effects were observed in both studies.

Vasquez et al. reported the use of intracameral bevacizumab in a patient with neovascular glaucoma and exudative retinal detachment following ^{125}I brachytherapy for a choroidal melanoma. The end result following the intracameral injection showed a resolution of the retinal detachment, and decrease of the intraocular pressure (with topical medication), however, the visual acuity did not improve [64].

Additional case reports describe improvement in the central subfield foveal thickness, ocular neovascularization and visual acuity after the injection of intraocular bevacizumab following ^{106}Ru and stereotactic radiotherapy [65–67].

Ranibizumab. Ranibizumab (Lucentis, Genentech, Inc) is a small antibody fragment synthesized to have an increased affinity (100 times greater) for all isoforms of VEGF-A, which reduces the vascular permeability and angiogenesis *in vivo* and *in vitro* [68]. Ranibizumab is US FDA approved for the treatment of choroidal neovascularization secondary to age-related macular degeneration [69].

Its use for the treatment of RR is also under study and seems to be promising. Dunavoelgyi et al. described a case of a 72-year-old patient with a juxtapapillary choroidal melanoma treated with sterotactic linear accelerator who developed medically uncontrolled neovascular glaucoma, optic neuropathy and a bullous retinal detachment with subretinal exudates. Intravitreal ranibizumab (0.05 mg) injection was followed by significant decrease in ocular neovascularization and a drop in intraocular pressure at two weeks and resolution of iris neovascularization and retinal detachment were evident at 24 weeks [70].

A recent phase 1, open-label, Genentech-sponsored study of five consecutive patients with RR related macular edema, secondary to the treatment with ^{103}Pd for uveal melanoma, showed visual acuity improvement in four of five patients and decrease in the foveal thickness in all cases after monthly intravitreal ranibizumab (0.5 mg) injections for at least four cycles [71].

Pepagtanib sodium. The first drug developed as a selective blocker of a VEGF isoform was pegaptanib sodium (Macugen, (OSI) Eyetech, Inc.). It acted as an anti-VEGF RNA aptamer that binds selectively to VEGF165 [72]. This drug was initially approved by the US FDA for the treatment of neovascular AMD, but has also been used in the treatment of proliferative diabetic retinopathy [73,74].

Recently, Querques et al. published a case of a 63-year-old woman who developed RR 14 months after the treatment with a ^{106}Ru episcleral plaque for a choroidal melanoma, characterized by capillary changes and retinal hemorrhages and exudates around the fovea. She was treated with laser photocoagulation but still developed neovascularization of the optic disc and retinal exudation involving the macula. Following intravitreal injection of 0.3 mg of pegaptanib sodium [Macugen; (OSI) Eyetech and Pfizer Inc., Melville, New York, USA], an improvement in the visual acuity and the macular exudation and optic disc neovascularization were observed at one month and maintained to the last follow-up (six months) [75].

Most of the studies published in the literature suggest that anti-VEGF agents may have a role in the treatment of radiation retinopathy, especially in the treatment of macular edema, and ocular neovascularization, although few studies demonstrate improvement in visual acuity. Because of the potential side effects, and the need for multiple injections to achieve sustained results, the role of bevacizumab and other anti-VEGF medications in the long-term management of radiation retinopathy has not been yet fully elucidated.

Other therapies

Application of some other modalities of treatment for radiation retinopathy, like hyperbaric oxygen therapy and oral pentoxifylline have been reported but more evidence is required to prove their efficacy and safety.

Hyperbaric oxygen therapy has shown success in the treatment of various ocular pathologies like vasculopathies, avascular scleral necrosis, vascular cystoid macular edema and radiation-induced optic neuropathies based on the concept that it improves oxygenation and acts as a sensitizer of hypoxic cells [76]. In terms of its use in radiation retinopathy, one reported case describes a 68-year-old woman with choroidal melanoma who developed ^{106}Ru-induced RR and optic neuropathy. The patient was treated with hyperbaric oxygen (2 h 100% O2 at 2 atm for 20 sessions) for two months with significant improvement in her visual field and fundus examination [77]. However, another report describing its use simultaneously with the radiotherapy revealed severe vaso-occlusion of the retinal vessels that might be due to a synergistic vasoconstrictive effect of hyperbaric oxygen and radiation [78].

Another reported therapeutic modality with favorable outcome is oral pentoxifylline. It is a methyl-xanthine derivative approved for the treatment of peripheral vascular diseases and thought to help in the management of radiation-induced fibrosis of soft tissues [79]. Its effect is based on the ability of the drug to cause vasodilation and decrease blood viscosity, thus improving blood flow and oxygenation. As for its use in radiation retinopathy, a report presents a 28-year-old woman who underwent stereotactic radiosurgery for the treatment of a left temporal lobe medulloblastoma and developed radiation retinopathy. Treatment with oral pentoxifylline (400 mg, 3 times daily) for eight months showed normal reperfusion of the capillary beds and significantly improved visual acuity [80].

Summary

Retinopathy is a significant cause of morbidity in patients treated with radiation. Established, successful long-term management strategies for this condition are lacking. Most of the current therapies have been copied from the treatment of other ischemic retinopathies especially diabetic retinopathy. However, the vascular damage observed in RR occurs at the level of the endothelial cells, while in diabetes the damage occurs mainly at the level of the pericytes, which may explain the poor results obtained in the treatment of RR [23,24].

Retinal photocoagulation remains the gold standard in the treatment of most forms of ischemic retinopathies. Although some reports demonstrate a beneficial effect for prophylactic photocoagulation in RR, larger randomized, controlled studies are needed to corroborate this hypothesis. In addition to that, not all patients treated with radiation will develop RR. This raises the question of whether prophylactically ablating the healthy surrounding retina would be justified. Alternative treatment options such as corticosteroids, have also been employed in the treatment of RR. A recent study that included 163 patients with uveal melanoma treated with ^{125}I plaque showed that periocular

injection of triamcinolone (40 mg/1 mL) given at the time of the plaque application and four and eight months later effectively reduced the risk of macular edema and moderate vision loss for 18 months [51].

Intravitreal anti-VEGF-A medications have been widely used in ischemic ocular diseases. There have been several studies, mostly case reports that showed a benefit in using these drugs in the treatment of RR. However, most of the currently used medications, such as corticosteroids, bevacizumab, ranibizumab and pegaptanib, only have a temporal effect, requiring multiple subsequent treatments. Currently, there is an ongoing interventional, randomized, single blinded study, the Treatment of Radiation Retinopathy Trial (TORR), on patients treated for uveal melanomas. The aim of the study is to demonstrate the superiority of intravitreal ranibizumab (0.5 mg) or triamcinolone acetonide (4.0 mg) treatment to no treatment, in the mean change from baseline in best-corrected visual acuity (http://clinicaltrials.gov/ct2/show/NCT00811200). This might offer more powerful clinical evidence about treatment options. However, an important point to take into consideration before treating patients with RR is that some have resolution of the ocular pathology without treatment making it difficult to judge the effect of the intervention. Undoubtedly, a multi-center collaborative effort will be needed in order to design clinical trials with sufficient statistical power to evaluate the safety, efficacy, and role of emerging pharmacotherapeutic agents. The development of preventive strategies remains paramount to avoidance of this potentially blinding condition.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Methods of Literature Search

A MEDLINE search of the English language literature from 1971 to present was conducted. The search terms used were: Radiation retinopathy, radiation maculopathy, choroidal melanoma, uveal melanoma, retinoblastoma, intracranial tumors, photodynamic therapy, laser photocoagulation, corticosteroids, bevacizumab, ranibizumab, pegaptanib, and VEGF inhibitors.

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